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Comparative effectiveness of catheter salvage strategies for pediatric catheter-related bloodstream infections*

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Abstract

Background—Intravascular catheter salvage may be attempted in clinically suitable cases in pediatric patients with catheter-related bloodstream infections. The purpose of this study was to assess the effectiveness of ethanol and hydrochloric acid (HCl) locks in achieving catheter salvage through decision-analysis modeling.

Methods—A Markov decision model was created to simulate catheter salvage using three management strategies: systemic antibiotics alone, antibiotics plus HCl lock, and antibiotics plus ethanol lock. One-way and two-way sensitivity analyses were performed for all model variables. Infection control rates and recurrence rates for each strategy were derived from prospective institutional data and existing pediatric literature. Costs were derived from institutional charges.

Results—With antibiotics alone, 73% of patients would require line replacement within 100 days, compared to only 31% and 19% of patients treated with HCl and ethanol lock, respectively. Incremental cost per additional catheter salvaged is \$89 for HCl lock and \$456 for ethanol lock. Superior efficacy of adjunct lock therapy is insensitive to changes in the anticipated duration of central access requirement and to clinically relevant variations in all model input variables.

Conclusion—HCl or ethanol locks are cost-effective adjuncts to systemic antibiotics for attempted catheter salvage in the setting of catheter-related bloodstream infections.

Keywords

Catheter-related bloodstream infection; Decision analysis; Cost-effectiveness; Ethanol lock; Hydrochloric acid lock

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Central venous catheter-related bloodstream infections (CR-BSI) are a significant source of morbidity within the critically and chronically ill pediatric populations [1,2]. Catheter removal and replacement has traditionally been considered vital for CR-BSI treatment, however, the Infectious Disease Society of America has acknowledged that certain patient subsets – including children – may be considered for catheter salvage therapy [3]. Because the incidence of thrombosis and stenosis following central venous catheterization may be up to 35%, effective protocols aimed at avoiding catheter replacement are critical.

A major contributor to the tenacity of CR-BSI's is the formation of microbial biofilms on the catheter surface. A biofilm is a three-dimensional extracellular matrix that can encase microbial communities. This protective structure renders the resident pathogens highly resistant to antimicrobial treatment [4,5]. High-concentration antibiotic lock therapy has been recognized for its role in catheter salvage. However, because drug penetrance through microbial biofilms is poor, antibiotic locks require prolonged dwell time (24–48 h) and drug concentrations 10×–1000× higher than those used for systemic therapy [6]. Moreover, certain antibiotics may actually induce biofilm formation [7], and concerns for resistance preclude the use of antibiotic locks for recurrent infections [8]. Given these limitations, there is pressing incentive to examine and implement alternative strategies for central venous catheter salvage.

Recently, ethanol (EtOH) and hydrochloric acid (HCl) locks have emerged as novel agents that nonspecifically denature biofilm protein, thereby facilitating infection control as adjuncts to systemic antibiotics [9,10]. Despite the fact that these agents are inexpensive, do not promote microbial resistance, and involve comparatively shorter dwell times, there is a paucity of data pertaining to their efficacy and cost-effectiveness. Thus far, retrospective and small prospective studies have shown promising rates of infectious control and low recurrence [11–16].

While not a substitute for a prospective, randomized clinical trial, a decision analysis approach can integrate data from multiple sources to propose recommendations for optimal, cost-effective care. A prime example exists in the comparison of video-assisted thoracoscopy versus tube thoracostomy and fibrinolytic therapy for pediatric empyema. A landmark cost-effectiveness analysis demonstrated that thoracostomy and fibrinolysis produced comparable utility and superior cost-efficacy compared to thoracoscopic surgery [17]. This finding was subsequently incorporated within committee recommendations by the American Pediatric Surgical Association [18], and influences practice to this day.

Ultimately, the decision to pursue catheter salvage in the setting of CR-BSI involves detailed reflection upon patient-specific factors (clinical stability, quality of life, socioeconomic factors). Because an evidence-based decision model cannot replicate this level of complexity, this study was designed not to determine *whether* salvage should be attempted, but rather, *which* salvage strategy is best, assuming that salvage is appropriate. Using decision-analysis, adjunct HCl and EtOH lock therapies were compared to systemic antibiotics alone in the setting of catheter salvage for pediatric CR-BSI. The *a priori* hypotheses were that both HCl and EtOH locks would be more efficacious than systemic

antibiotics alone, and that HCl lock would be more cost-effective than EtOH lock because of a shorter standard dwell time.

1. Materials and methods

1.1. Model design

A Markov decision model was created to simulate a pediatric patient found to have bacterial CR-BSI who has an anticipated future central venous access requirement of 100 days [19]. These decision models are used in comparative effectiveness studies to calculate the expected costs and utilities of two or more interventions. Markov models are mathematical simulations in which patients in compared intervention groups transition to alternative health states depending on the occurrence of potential outcomes. Following initial therapy, patients are followed for a prespecified number of Markov cycles, with each cycle representing a unit of time (i.e., a week, a month, a year). Each Markov cycle is characterized by a health state, and patients may remain in the same health state or transition to a new health state at the end of each cycle. The likelihood of transitioning between different health states is captured by transition rate variables. Each health state is associated with a cost that represents the state's financial burden over one cycle. Thus, a Markov model simulates treatment and posttreatment progression in a time-dependent manner, and assigns efficacy and cost based on the number of cycles that each patient spends within each health state.

For this study, a hypothetical patient with a diagnosis of CR-BSI undergoes attempted catheter salvage using one of three treatment strategies: A) broad-spectrum systemic antibiotics, B) antibiotics plus adjuvant 70% EtOH lock, and C) antibiotics plus 2 M HCl lock. A 10-day course of systemic antibiotics (vancomycin and piperacillin–tazobactam) was modeled. Ethanol locks are administered with 12- to 24-h dwell time for three consecutive days, during which peripheral venous access is required [9,13]. Hydrochloric acid lock administration is performed according to protocols described by Barbaric et al. [11], requiring a total of 1.5 h per treatment.

Following attempted salvage, infection control is defined by presence of a negative blood culture within 48 h of initial CR-BSI diagnosis. Those patients who achieve infection control are monitored for recurrence. Each Markov cycle in the monitoring period represents 10 days, thus, the model proceeds for 10 cycles. Should CR-BSI recur, the patient may undergo repeat salvage attempts. Patients who do not achieve infection control for index or recurrent CR-BSI undergo catheter replacement (Fig. 1). The model's primary outcome is the likelihood of retaining the index catheter for 100 days (successful salvage). The secondary outcome is cost per catheter salvaged.

1.2. Transition rates

For each treatment arm, there are three relevant transition rates. Infection control rate is the likelihood of having a negative blood culture within 48 h of initial CR-BSI diagnosis. Because rate of infectious recurrence following salvage changes over time, two unique variables were used to represent time-dependent recurrence rates over two time periods after infection control: days 1–30 and days 31–100. Time-dependent rate of recurrence for each Markov cycle was extrapolated from these variables.

To obtain variable baseline estimates, a literature review was performed for pediatric articles published within the past 15 years pertaining to salvage outcomes for CR-BSI. Infection control rates were estimated as weighted averages from these published data (Table 1). Similarly, 30-day recurrence rates were extrapolated from existing literature for EtOH lock and HCl lock regimens. Over the past 15 years, no adequately sized study has documented time-dependent, recurrence-free catheter survival for 100 days following salvage using any treatment strategy. To address this limitation, an assumption was first made that the beneficial effect of adjuvant locks does not extend beyond 30 days posttreatment. Thus, we anticipate that the rate of recurrent infection following initial salvage is equivalent across the three treatment modalities for days 31–100. We then queried a prospectively collected institutional database of all pediatric CR-BSI for cases of attempted catheter salvage. Neither HCl lock nor EtOH lock was used within this series. Initial infection control rate using systemic antibiotics alone was 57% (59/104), comparable to outcomes from existing literature [20–22]. Using this sample, recurrent CR-BSI was identified through chart review, and time-dependent rate of recurrence was derived through Kaplan–Meier analysis (Fig. 2). Through these methods, we obtained an estimate for infection recurrence rate over days 31–100 following an initially successful salvage, and applied this estimate to all three model treatment arms.

1.3. Costs

Cost variables for broad-spectrum antibiotics, EtOH and HCl lock therapies, temporary peripheral vascular access, and central venous catheter replacement were derived from institutional charges (Table 1). Because total charges for tunneled permanent central venous catheters vary by operative complexity and anesthesia costs, the charge for a peripherally inserted central catheter (PICC) was used as a conservative estimate.

This study was approved by the University of Virginia Institutional Review Board (protocol #16171).

1.4. Statistical analysis

The model's primary outcome was assessed for the baseline scenario and for scenarios involving shorter and longer periods of anticipated access. Cost-effectiveness was measured as cost per catheter salvaged, equivalent to the total cost of treating one infected catheter divided by the likelihood of successful salvage at 100 days. The incremental cost-effectiveness ratio (ICER) for each lock therapy was defined as the cost per additional catheter salvaged, compared to a salvage regimen involving systemic antibiotics alone. One-way and two-way sensitivity analyses were performed for all model variables across wide ranges of potential values. Because the alternative to salvage is immediate replacement, the willingness-to-pay (WTP) threshold was parsimoniously set at the cost of PICC line insertion (\$2200).

2. Results

Likelihood of salvage for 100 days was 27%, 69%, and 81% for antibiotics alone, antibiotics plus HCl lock, and antibiotics plus EtOH lock, respectively. The cost per catheter salvaged

for each protocol is listed in Table 2. Notably, for 100 days of anticipated access, the cost of salvaging a catheter using an antibiotics-only strategy is \$2456, higher than the WTP threshold (\$2200). Compared to salvage using antibiotics alone, the ICERs for adjuvant HCl lock and EtOH lock are \$87 and \$453 per additional catheter salvaged, respectively, both less than the WTP threshold. Comparing the two adjuvants, EtOH lock is more effective but also more costly, with an ICER of \$1744 per additional catheter salvaged over HCl lock.

The baseline model was repeated for scenarios requiring between 10 days and 300 days of anticipated central access (Table 2). Results suggest that, for patients requiring more than 80 days of central access, an antibiotics-only salvage regimen is more costly than immediate catheter replacement. By comparison, adding either EtOH lock or HCl lock makes salvage cost-effective for patients with anticipated access requirements of up to 200 days. For patients requiring 300 days of access or more, immediate replacement has lower expected direct costs than any of the salvage strategies.

Threshold values from one-way sensitivity analyses comparing HCl lock or EtOH lock versus antibiotics-only salvage are shown in Table 2. For example, antibiotics alone is more cost-effective than antibiotics plus HCl lock if the infection control rate for HCl lock is lower than 36% (80% reported). The cost-effectiveness of either lock therapy compared to antibiotics alone was robust to all model variables. Because the baseline ICER of EtOH lock relative to HCl lock closely approximates WTP, sensitivity analyses between these protocols were not performed out of recognition that relative cost-effectiveness would be sensitive to all model variables. Two-way sensitivity analyses comparing both lock adjuvants to antibiotics alone are shown in Fig. 3.

3. Discussion

Results of this decision model support the addition of HCl lock or EtOH lock to systemic antibiotics for attempted catheter salvage. Both adjuvants are cost-effective compared to antibiotics alone. This advantage is present for anticipated duration of central access up to 200 days. For patients with central access needs of 300 days or more, immediate catheter replacement is more cost-effective than attempted salvage with or without HCl or EtOH treatments. Because the ICER of EtOH lock compared to HCl lock approximates the cost of a new catheter, the two lock therapies may be considered equally cost-effective. However, this last finding is based on a parsimonious WTP threshold derived from the charge of a PICC line. For cases with a higher WTP – i.e., if an operative tunneled line is indicated – EtOH lock may be more cost-effective than HCl lock because of its reportedly lower recurrence rate [14–16].

Sensitivity analyses indicate that the model's main finding – that lock therapies are cost-effective compared to antibiotics alone – is robust to potential changes in each variables' baseline estimates. For all variables, one-way sensitivity thresholds fell outside the range of values reported in recent literature, and outside of clinically realistic values, thereby reinforcing the validity of the model's predictions. For example, antibiotics alone is more cost-effective than antibiotics plus adjuvant HCl lock if the infection control rate of adjuvant HCl lock is lower than 36% (Table 1). However, the infection control rate of antibiotics

alone is 55%. Based on its mechanism of action, it is exceedingly unlikely that adding HCl lock would paradoxically reduce infection control. Scrutiny of each of the other transition variables – i.e., recurrence free line survival at 30 and 100 days for each strategy – revealed similarly implausible sensitivity thresholds.

The effectiveness of lock therapies within this model is driven by an increase in rate of infection control. Even among patients with CR-BSI refractory to systemic antibiotics, HCl lock may attain infection control in more than 67% of cases [11,13]. Furthermore, while antibiotic-mediated salvage is ineffective against fungal CR-BSI, both HCl and EtOH locks have efficacy against catheter-associated fungemia [15]. Because fungal infections were not included in the present model, the true benefit of adjuvant lock therapy may be underestimated. Finally, avoiding catheter replacement through salvage decreases the risk of venous stenosis, thrombosis, operative anesthesia and mechanical complications of replacement. These downstream benefits of catheter salvage are not included in this model, and likely provide further incentive to adopt biofilm-targeting adjuvants. Therefore, while model costs were estimated through hospital charges that may vary across institutions, these intangible benefits of catheter salvage increase the likelihood of lock therapy's cost-effectiveness.

This study has several limitations. First, HCl and EtOH locks were not compared to high-dose antibiotic lock, which is associated with a 40%–93% infection control rate [8,23–25]. Because its effectiveness is pathogen-specific, modeling high-dose antibiotic lock requires assumptions regarding pathogen distribution which vary greatly by institution. Further, because of concerns for mounting resistance, antibiotic lock may not be justified for recurrent CR-BSI, whereas recurrence is treatable by HCl or EtOH lock. Second, clinical utility was not incorporated in the model. Factors such as clinical stability may dictate that catheter salvage is not an option. Therefore, this model's role was to compare salvage strategies; determining whether a patient is suitable for salvage is a different and complex inquiry deserving further study. Third, the rate of recurrent infection following catheter replacement was not accounted for in this model, because this value is thus far poorly understood. An evidence-based estimate – but likely an underestimate – may be the infection rate of a new catheter, which is reportedly 5–10 cases per 1000 catheter-days [26]. Incorporating this estimate into a modified decision model did not significantly alter the relative cost-effectiveness of the three strategies. Finally, potential adverse effects of therapy were not included. Flushing EtOH into the circulation has been associated with transient dyspnea and nausea [9]. Flushing HCl can result in a transient febrile reaction in a minority of patients [27]. However, diligent technique in aspirating the solution effectively minimizes these risks [15,28]. Although EtOH can induce protein precipitation from plasma in vitro [29], catheter occlusion has not been reported. Scanning electron microscopy has demonstrated that no structural degradation occurs following prolonged catheter exposure to HCl [30].

4. Conclusions

Existing evidence supports augmenting systemic antibiotics with adjuvant HCl or EtOH lock therapy for attempted central venous catheter salvage in the setting of CR-BSI. Both

adjuvants are cost-effective for anticipated access durations of up to 200 days. While EtOH lock has a higher salvage rate than HCl lock, it is also more costly, and may be more appropriate for patients with surgically placed, long-term catheters.

Abbreviations

CR-BSI	catheter-related bloodstream infection
EtOH	ethanol
HCl	hydrochloric acid
ICER	incremental cost-effectiveness ratio
PICC	peripherally inserted central catheter
WTP	willingness-to-pay

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Appendix A. BAPS discussion

Yinin Hu (Charlottesville VA)

Q: Joe Curry, London GOSH This is very important information, thank you. I was just going to ask if you knew what organisms were more likely to be producing a recurrent infection to guide the clinician in whether to remove the line or go for salvage.

A Yinin Hu Unfortunately, our sample size is not big enough to answer that, but other studies have suggested coagulase-negative staphylococci spp. are associated

with recurrent infection. The impetus for this catheter database was that bio-film targeting agents can actually disrupt the biofilm, and it should render every catheter able to have a salvage attempt.

Q: Niyi Ade-Ajayi, London, King's College Hospital We are about to publish a technique of vein preservation involving treating with antibiotics, taking the old catheter out from within the sheath, and re-inserting using the same tunnel or sheath as an alternative. Is that practice a part of your unit's strategy?

A Yinin Hu Normally, whether or not we re-insert the catheter in the same site or different site is a point of discussion with the service who is primarily taking care of the patient. Generally, if the patient is immune-suppressed, we will generally try a different site. In patients with intestinal failure who really have to have their access preserved then maybe a more pragmatic, and similar, approach is taken and the site is used for as long as possible.

Fig. 1.

Markov model for treatment of bacterial catheter-related bloodstream infection (CR-BSI) using antibiotics alone, antibiotics plus ethanol lock, or antibiotics plus hydrochloric acid (HCl) lock. Patients who fail to attain infection control (culture negative within 48 h) proceed to catheter replacement.

Fig. 2. Kaplan–Meier curve representing infection recurrence-free catheter survival after successful salvage using antibiotics alone. Data are censored for noninfectious catheter removal.

Fig. 3.

Two-way sensitivity analyses for transition variables, comparing systemic antibiotics only versus antibiotics plus ethanol lock (EtOH, left) or antibiotics plus hydrochloric acid lock (HCl, right). Variables assessed include the infection control rate (IC rate) and recurrence-free rate at 100 days (RFS). Black markers indicate baseline variable estimates. Graphs indicate superiority of antibiotics alone (gray) or antibiotics plus lock therapy (white). Sensitivity thresholds are represented as the gray/white interface. Baseline estimates are uniformly in favor of adjunctive lock therapy, and are relatively distant from the sensitivity thresholds. This suggests that the model's results are relatively robust to potential uncertainties in baseline parameter estimates. RFS: infection recurrence-free rate (at day 100); IC: infection control.

Table 1

Model variables and one-way sensitivity thresholds.

Variable	N	Baseline value	Reported range	Sensitivity threshold	Reference
Infection control rate					
Antibiotics-only	229	0.55	0.42–0.57	0.93	[20–22]
Abx + HCl lock	100	0.80	0.67–0.85	0.36	[11,12]
Abx + EtOH lock	87	0.87	0.50–0.94	0.43	[13–16]
RFS (days 1–30)					
Antibiotics-only	53	0.38	0.00–1.00*	1.00	Institutional
Abx + HCl lock	100	0.75	0.75–0.76	0.24	[11,12]
Abx + EtOH lock	98	0.87	0.35–1.00	0.34	[9,13–15]
RFS (days 31–100)					
All protocols	53	0.47	–	–	Institutional
Costs					
Vancomycin (10 d)		\$55.5			Institutional
Pip-Tazo (10 d)		\$350.8			
EtOH lock		\$160.4			
HCl lock		\$53.5			
Peripheral access		\$54.0			
Catheter repl.		\$2200.0			

Abx: intravenous antibiotics; HCl: hydrochloric acid; EtOH: ethanol; Pip-Tazo: piperacillin-tazobactam.

*Wide range adopted due to institutional data source.

Table 2

Cost-effectiveness of catheter salvage given anticipated duration of access.

Salvage protocol	Salvage rate	Cost per salvage	ICER (vs Abx only)
10-day			
Antibiotics only	55.0%	\$739	
HCl + Abx	80.0%	\$570	\$200
EtOH + Abx	87.0%	\$713	\$670
50-day			
Antibiotics only	37.0%	\$1546	
HCl + Abx	76.0%	\$724	<\$0
EtOH + Abx	86.0%	\$800	\$236
80-day			
Antibiotics only	30.0%	\$2109	
HCl + Abx	72.0%	\$891	\$21
EtOH + Abx	83.0%	\$996	\$366
100-day*			
Antibiotics only	27.0%	\$2457	
HCl + Abx	69.0%	\$1015	\$87
EtOH + Abx	81.0%	\$1123	\$453
200-day			
Antibiotics only	15.0%	\$5135	
HCl + Abx	58.0%	\$1,666	\$456
EtOH + Abx	73.0%	\$1782	\$915
300-day			
Antibiotics only	8.0%	\$10,368	
HCl + Abx	48.0%	\$2473	\$894
EtOH + Abx	65.0%	\$2542	\$1444

ICER: incremental cost-effectiveness ratio; Abx: intravenous antibiotics; HCl: hydrochloric acid lock; EtOH: ethanol lock.

* Baseline model.