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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.
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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

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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.

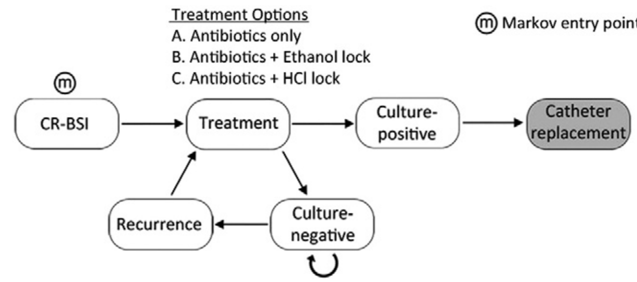

Fig. 1. Markov model for treatment of bacterial catheter-related bloodstream infection (CR-BSI) using antibiotics alone, antibiotics plus ethanol lock, or antibiotics plus hydrochloric acid (HCl) lock. Patients who fail to attain infection control (culture negative within 48 h) proceed to catheter replacement.

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

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