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CVCB Antimicrobial Lock Therapy Study

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Abstract

Medical researchers at Department of Infectious Diseases and Microbiology at the Stamford Hospital in Stamford, CT are studying episodes of central venous catheter-related bacteremia (CVCB) that have become common events in patients with long-term indwelling central venous catheter use. Since no standardized treatment of CVCB exists, novel approaches have been used to salvage infected catheters where vascular access is limited. Use of antibiotic lock solutions (e.g., a solution of an antibiotic agent and heparin) to fill catheter lumens between treatments (antibiotic-lock treatment, ALT) has been shown to prevent CVCB and may be useful for treatment of already-infected catheters. In this report we analyze the success of ALT in preventing CVCB.

1 Introduction

This study aims to investigate the success of ALT in preventing CVCB. The researchers retrospectively examined patient records over a ten-year period to evaluate effectiveness of antibiotic lock solutions for catheter salvage in patients experiencing CRB to determine what criteria might be useful for clinicians deciding between ALT and device removal.

Out of 458 episodes of CVCB, ALT was attempted in 116 cases (25.3%). Of these, successful salvage was attained in 86 cases (74.1%) while 30 attempts at salvage (25.9%) failed. Treatment effectiveness varied widely based on organism ranging from 78.9% (15/19) for Gram-negative bacilli, to 42.8% (9/21) for Staphylococcus aureus (including MRSA) infections.

Of the 116 cases, only 87 are unique patients. A few patients appear multiple times, some with different diagnoses. The clients viewed each catheter episode as a separate, distinct event and would rather count each "episode" rather than each "patient" as several patients presented at different dates with different/replaced catheters, etc. The clients suggested that they are measuring the success of treating each catheter (clearing it of infection), not of each patient's ultimate outcome since a failure in the study was not necessarily the death of a patient, but rather the removal/loss of that patient's catheter as a direct result of persistent infection.

In our analysis we have assumed that each episode is an independent event however we also performed the analyses with the repeated patients omitted to see if they meaningfully influenced the results.

In this report we aim to answer the following research questions based on this data set:

1. Is the lower success rate for Staph aureus infections compared to all other organisms statistically significant?
2. Is age a significant factor on treatment success?
3. Is there a significant difference in the rate of success between inpatient and outpatient onset?
4. Is duration of treatment a significant factor on treatment success?

2 Methodology

All analyses were done using `R` statistical software. For questions (1) and (3) where rate of success was compared for two groups Pearson's χ^2 test was performed using the `prop.test` function in `R`.[1] For questions (2) and (4) a binomial generalized linear model with a logit link was fit using the `glm` function in `R`.[2]

3 Results

Results for each research question are presented below.

3.1 Is the lower success rate for Staph aureus infections compared to all other organisms statistically significant?

In order to answer this question we compared the success rate for the Staph aureus infections with the success rate of the other types of infections combined. Using a Pearson's χ^2 test, the hypotheses that we tested were:

H_0 : Success rate in the Staph aureus and other infections groups are equal

H_A : Success rate in the Staph aureus group is lower than the success rate in the other infections group

As per request of the client we performed the analysis two ways: (1) include MRSA in the Staph aureus group and (2) exclude MRSA from the Staph aureus group.

3.1.1 Including MRSA in the Staph aureus group

Including MRSA in the Staph aureus group, there were 9 successes in 21 treatments. For the other groups there were 77 successes in 95 treatments. The data used for the hypothesis test is given in Table 1.

Table 1: Distribution of successes and failures in Staph aureus (including MRSA) and other infections groups

	Staph aureus (including MRSA)	Other	Total
Success	9	77	86
Failure	12	18	30
Total	21	95	116

A hypothesis test suggests that the rate of success in the Staph aureus group was significantly lower than the other group with a p-value of approximately 0.0004 ($\chi^2 = 11.1697$, df = 1).

3.1.2 Excluding MRSA from the Staph aureus group

Not including MRSA in the Staph aureus group, there were 7 successes in 18 treatments. In the other groups there were 79 successes in 98 treatments. The data used for the hypothesis test is given in Table 2.

Table 2: Distribution of successes and failures in Staph aureus (not including MRSA) and other infections groups

	Staph aureus	Other	Total
Success	7	79	86
Failure	11	19	30
Total	18	98	116

A hypothesis test suggests that the rate of success in the Staph aureus group is significantly lower than the other group with a p-value of approximately 0.0003 ($\chi^2 = 11.7165$, df = 1).

It should be noted that one of the conditions of a χ^2 test is that expected counts need to be greater than or equal to 5 and the expected number of failures for the Staph aureus group was 2.84 ($30 \cdot 28/116$) in this case. Since this condition was not satisfied the χ^2 approximation may not be reliable. However, as the p-value is very small the approximation is unlikely to affect the outcome of the hypothesis test.

The results were still significant when repeated patients were omitted from the analysis with a p-value of approximately 0.0004 when MRSA is included in the Staph aureus group and a p-value of approximately 0.0003 when MRSA is not included in the Staph aureus group. Output for this analysis is provided in Appendix A.

3.2 Is age a significant factor on treatment success?

We used a binomial generalized linear model with a logit link where the response variable was whether or not the treatment was successful and the explanatory variable was age to test the following set of hypotheses:

$$H_0 : \beta_{Age} = 0 \text{ (Age is not a significant factor on treatment success)}$$
$$H_A : \beta_{Age} \neq 0 \text{ (Age is a significant factor on treatment success)}$$

The output for the generalized linear model is given in Table 3.

Table 3: GLM for treatment success vs. age

	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	-0.6058	0.8362	-0.72	0.4688
Age	0.0271	0.0136	2.00	0.0454

With a p-value of 0.0454, age appears to be a marginally significant predictor for treatment success at $\alpha = 0.05$. A coefficient of 0.0271 indicates that when age increases by 1 unit, the odds of treatment success increases by $e^{\beta_{age}} = e^{0.0271} = 1.027$.

When repeated patients were omitted age is no longer a significant predictor for treatment success with a p-value of 0.34. The output for the generalized linear model with repeated patients omitted is given in Appendix B. This suggests that even if there is a significant connection between age and success it is very weak, and should be checked with additional data if possible.

3.3 Is there a significant difference in the rate of success between inpatient and outpatient onset?

In order to answer this question we compared the success rate for the inpatient onset group with the success rate of the outpatient onset group. Using a Pearson's χ^2 test, the hypotheses that we tested were:

$$H_0 : \text{Success rate in the inpatient and outpatient onset groups are equal}$$
$$H_A : \text{Success rate in the inpatient and outpatient onset groups are different}$$

In the outpatient onset group there are 69 successes in 95 treatments and in the inpatient onset group there were 13 successes in 14 treatments. There were 7 observations (3 failures and 4 successes) for which onset location was missing, they have been omitted from this analysis. The data used for the hypothesis test is given in Table 4.

Table 4: Distribution of successes and failures based on onset location

	Outpatient	Inpatient	Total
Success	69	13	82
Failure	26	1	27
Total	95	14	109

The hypothesis test suggests that the rate of success in the inpatient and outpatient groups were not significantly different with a p-value of 0.1919 ($\chi^2 = 1.7031, df = 1$). It should be noted the χ^2 value calculated may not be accurate due to the low count for for inpatient failures. However, as the p-value was not close to the cutoff it is unlikely that this difference will be significant even if more data is collected.

With repeated patients omitted the difference between the rates of success in the inpatient and outpatient groups was also not significant with a p-value of 0.5099. Output for this analysis is provided in Appendix C.

3.4 Is duration of treatment a significant factor on treatment success?

We used a binomial generalized linear model with a logit link where the response variable is whether or not the treatment was successful and the explanatory variable was duration of treatment to test the following set of hypotheses:

$$H_0 : \beta_{Dur} = 0 \text{ (Duration of treatment is not a significant factor on treatment success)}$$
$$H_A : \beta_{Dur} \neq 0 \text{ (Duration of treatment is a significant factor on treatment success)}$$

The output for the generalized linear model is given in Table 5.

Table 5: GLM for treatment success vs. treatment duration

	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	0.8454	0.3272	2.58	0.0098
Lock.Duration	0.0168	0.0210	0.80	0.4226

With a p-value of 0.4226, treatment duration was not a significant predictor for treatment success. We also attempted to fit more complex models involving age and onset location and even when combined with these other predictors there was no significant duration effect.

When repeated patients were omitted the treatment duration was not a significant predictor for treatment success with a p-value of 0.186. The output for the generalized linear model with repeated patients omitted is given in Appendix D.

4 Summary

We found that treatment success rate was significantly lower for the Staph aureus group (both including and not including MRSA) than the other infection groups however the difference between the success rates for inpatient and outpatient onset is not statistically significant.

Additionally, age is a marginally significant predictor for treatment success, while treatment duration is not.

5 References

[1] http://stat.ethz.ch/R-manual/R-patched/library/stats/html/prop.test.html.

[2] http://stat.ethz.ch/R-manual/R-patched/library/stats/html/glm.html.

A Comparing success rate in Staph aureus and other infections groups - omitting repeated patients

A.1 MRSA included in the Staph aureus group

```
2-sample test for equality of proportions with continuity correction

data:  c(sa.mrsa.sucU, sa.mrsa.oth.sucU) out of c(sa.mrsa.trU, sa.mrsa.oth.trU)
X-squared = 11.4288, df = 1, p-value = 0.0003616
alternative hypothesis: less
95 percent confidence interval:
 -1.0000000 -0.1867265
sample estimates:
  prop 1   prop 2
0.437500 0.882353

Warning message:
In prop.test(x = c(sa.mrsa.sucU, sa.mrsa.oth.sucU), n = c(sa.mrsa.trU,  :
  Chi-squared approximation may be incorrect
```

A.2 MRSA not included in the Staph aureus group

```
2-sample test for equality of proportions with continuity correction

data:  c(sa.sucU, sa.oth.sucU) out of c(sa.trU, sa.oth.trU)
X-squared = 11.57, df = 1, p-value = 0.0003351
alternative hypothesis: less
95 percent confidence interval:
 -1.0000000 -0.2037016
sample estimates:
   prop 1    prop 2
0.3846154 0.8703704

Warning message:
In prop.test(x = c(sa.sucU, sa.oth.sucU), n = c(sa.trU, sa.oth.trU),  :
  Chi-squared approximation may be incorrect
```

B Age as a predictor for treatment success - omitting repeated patients

	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	0.2209	1.0912	0.20	0.8396
Age	0.0163	0.0171	0.95	0.3403

C Comparing success rate in inpatient and outpatient groups - omitting repeated patients

```
2-sample test for equality of proportions with continuity correction

data:  c(home.sucU, hosp.sucU) out of c(home.trU, hosp.trU)
X-squared = 0.4343, df = 1, p-value = 0.5099
alternative hypothesis: two.sided
95 percent confidence interval:
 -0.4323286  0.1232377
sample estimates:
   prop 1    prop 2
0.7454545 0.9000000

Warning message:
In prop.test(x = c(home.sucU, hosp.sucU), n = c(home.trU, hosp.trU),  :
  Chi-squared approximation may be incorrect
```

D Duration as a predictor for treatment success - omitting repeated patients

	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	0.7276	0.4551	1.60	0.1099
Lock.Duration	0.0455	0.0344	1.32	0.1857