15-20 Methodological and Statistical Issues

56 Importance of Qualified Biostatistical Study Input

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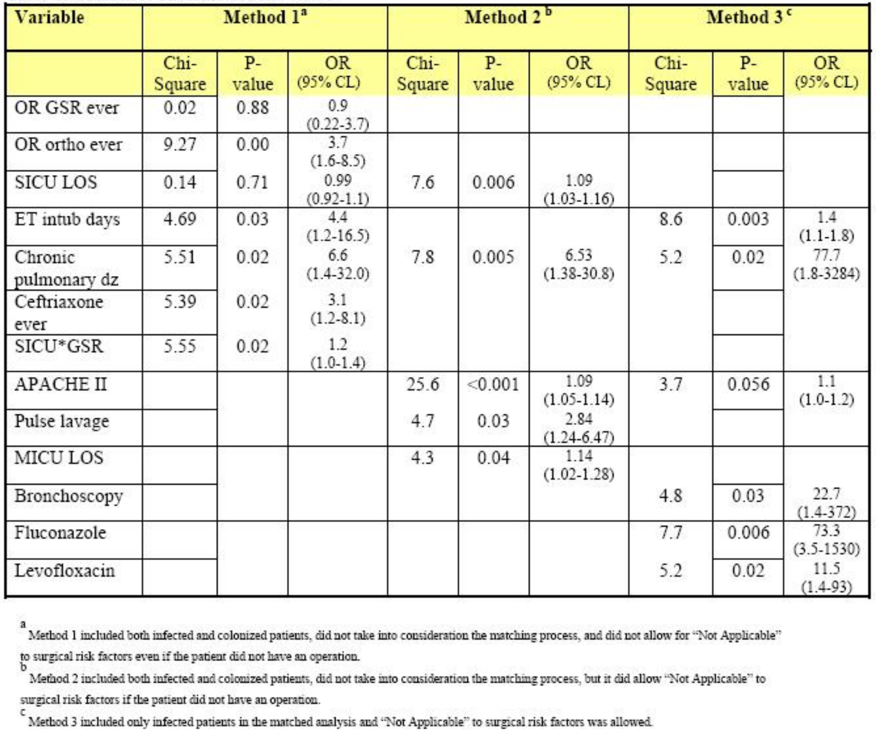
Background: Inappropriate analytic methods can drastically change the conclusions of a study and adversely affect the scientific message. Medical schools now incorporate a few hours of biostatistics into the core curriculum. This brief venture into the methods of research design may lead clinicians into believing that they have the necessary skill to complete their own analyses, when in fact this is an incorrect assumption.

Objective: Data from a case control study of an Acinetobacter baumannii (AB) outbreak will be used to illustrate the hazards of a lack of statistical acumen on the conclusions of a study.

Methods: We conducted a study to investigate a clonal outbreak of multi-drug resistance AB in the surgical intensive care unit. Cases were defined as patients with AB on a lab isolate over a nine month period (December 1, 2004 to August 31, 2005). Cases were matched 1:1 with concurrently hospitalized controls without AB. A total of 152 subjects were enrolled in the study. Out of the 76 cases, 67 were infected with AB while nine were colonized with AB. The investigators were interested in evaluating risk factors for this infection, describing its clinical manifestations, and predicting outcomes. Multiple logistic regression models were used in all three analyses.

Results: The initial method included both infected and colonized patients (n=152). The data were analyzed without taking into consideration the matching process. Any patient who did not answer "yes" to a surgical risk factor was considered to not have that risk factor. There were 7 significant predictors of case status: operation by general surgery (GS) or orthopedics, SICU length of stay (LOS) prior to infection, days intubated, history of chronic pulmonary disease (COPD), ceftriaxone use, and LOS*GS interaction (Table 1). The second method included both infected and colonized patients, and matching was not considered. However, this analysis did allow "Not Applicable" for surgical risk factors if a patient did not have any surgeries. There were 5 significant predictors in this model: SICU LOS, COPD, APACHE II score, pulse lavage, and MICU LOS. The third method limited the cohort to infected patients and accounted for the matching process (n=62 pairs). Any surgical predictor that was not applicable was set to missing. There were 6 significant predictors by this model: days intubated, COPD, APACHE II score, bronchoscopy, fluconazole, and levofloxacin.

Table 1. Predictors of Acinetobacter status



Variable	Method 1[a]			Method 2[b]			Method 3[c]		
	Chi-Square	P-value	OR (95% CL)	Chi-Square	P-value	OR (95% CL)	Chi-Square	P-value	OR (95% CL)
OR GSR ever	0.02	0.88	0.9 (0.22-3.7)						
OR ortho ever	9.27	0.00	3.7 (1.6-8.5)						
SICU LOS	0.14	0.71	0.99 (0.92-1.1)	7.6	0.006	1.09 (1.03-1.16)			
ET intub days	4.69	0.03	4.4 (1.2-16.5)				8.6	0.003	1.4 (1.1-1.8)
Chronic pulmonary dz	5.51	0.02	6.6 (1.4-32.0)	7.8	0.005	6.53 (1.38-30.8)	5.2	0.02	77.7 (1.8-3284)
Ceftriaxone ever	5.39	0.02	3.1 (1.2-8.1)						
SICU*GSR	5.55	0.02	1.2 (1.0-1.4)						
APACHE II				25.6	<0.001	1.09 (1.05-1.14)	3.7	0.056	1.1 (1.0-1.2)
Pulse lavage				4.7	0.03	2.84 (1.24-6.47)			
MICU LOS				4.3	0.04	1.14 (1.02-1.28)			
Bronchoscopy							4.8	0.03	22.7 (1.4-372)
Fluconazole							7.7	0.006	73.3 (3.5-1530)
Levofloxacin							5.2	0.02	11.5 (1.4-93)

[a] Method 1 included both infected and colonized patients, did not take into consideration the matching process, and did not allow for "Not Applicable" to surgical risk factors even if the patient did not have an operation.

[b] Method 2 included both infected and colonized patients, did not take into consideration the matching process, but it did allow "Not Applicable" to surgical risk factors if the patient did not have an operation.

[c] Method 3 included only infected patients in the matched analysis and "Not Applicable" to surgical risk factors was allowed.

Conclusions: None of the identified risk factors were significant predictors in all three models. Only the third method should be used for a matched case-control study in an infectious disease outbreak. The dramatically different conclusions demonstrate why it is important to analyze data with the appropriate methodology and to involve a trained biostatistician in the study.

57 Small Area Estimation of Mandatory Surveillance for Methicillin Resistant *Staphylococcus aureus* (MRSA)

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Background: The voluntary reporting of *Staphylococcus aureus* demonstrated a year on year rise from 1990. Concerns about this increase led the English Department of Health (DH) to introduce mandatory reporting of methicillin resistant (MRSA) and sensitive (MSSA) *Staphylococcus aureus* bacteraemia in April 2001. Against this backdrop, as of 2004 a performance target for a 50% reduction in the numbers of MRSA bacteraemia was set for April 2008.
All acute trusts (n=172) in England are required to participate in the mandatory reporting programme. Increasingly, the DH and other regulatory bodies are assessing Trust performance against performance targets, benchmarking mechanisms, and performance indicators. This invariably leads to assessing trust performance based on small counts. Classical direct estimation approaches are based on large sample size and produce a reliable estimate of MRSA at national level. However, there is growing demand for similar estimates at small areas (at trust, hospital in our application) level. The small number of MRSA cases limits the application of direct estimation methods.

Objective: To develop an alternative statistical technique for estimating MRSA bacteraemia at small area level.

Methods: We introduce a model-based (indirect) approach that uses auxiliary information for the small areas and has been characterized in the statistical literature as “borrowing strength” from the relationship between the values of the variables and the auxiliary information. The approach is called Small Area Estimation (SAE) and has power to produce more precise estimates not only for small areas (trust or hospital) with small cases but also for small areas without any cases.

Results: We present an application of the method to MRSA data for the period 2001 to 2006 collected through the mandatory surveillance scheme. We also compare the different approaches and present a limited simulation results that support our method.

Conclusions: The results indicate that the proposed method has the potential to lead to substantial increases in estimation efficiency compared to the direct and synthetic approaches. The gain in efficiency becomes even clearer for the trusts with small number of MRSA bacteraemias and estimates are approached to an unbiased direct estimate for large numbers of MRSA bacteraemias. The standardisation and target/threshold setting are two other recent applications of the method.

58 Controlling for Severity of Illness in Assessing the Association between Antimicrobial-Resistant Infection and Mortality: Impact of Calculating APACHE II Score at Different Time Points

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Background: In studies of the association between antibiotic-resistant infection and mortality, the importance of controlling for underlying severity of illness is well recognized. However, it is unclear when severity of illness should be assessed relative to the infection. Controlling for severity of illness on the day of infection may underestimate the true association between resistance and mortality.

Objective: To assess the impact of calculating severity of illness (using the APACHE II score) on different days on the association between resistance and mortality.

Methods: We used an existing dataset from a study investigating the association between fluoroquinolone resistance and mortality (*Clin Infect Dis* 2005;41:923-9). The APACHE II score was calculated at three time points: 1) the day of culture; 2) the day prior to culture; and 3) two days prior to culture. Separate multivariable models were constructed using the three different APACHE II scores. These models were compared qualitatively.

Results: Among 91 subjects, 51 had a FQ-resistant infection and 40 had a FQ-susceptible infection. The median (95%CI) APACHE II score for all subjects was 13 (11-15) when calculated on the day of culture, 12 (11-13) one day prior to culture, and 11 (10-13) two days prior to culture. The three multivariable models (each using APACHE II score calculated on a different day) were not substantively different (Tables 1-3).

Conclusions: APACHE II scores calculated at different time points relative to infection did not differ substantively. Furthermore, when assessing the adjusted association between FQ resistance and mortality, there were no substantive differences across multivariable models incorporating APACHE II calculated at different time points.

Model with APACHE II calculated on day of culture

Variable	**Adjusted OR (95%CI)**	**p value**
FQ-resistant infection	1.65 (0.34, 8.05)	0.54
APACHE II score	1.15 (1.04, 1.27)	0.005
Race (African-American)	0.31 (0.07, 1.38)	0.12

Model with APACHE II calculated one day prior to culture

Variable	**Adjusted OR (95%CI)**	**p value**
FQ-resistant infection	1.41 (0.27, 7.51)	0.68
APACHE II score	1.16 (1.03, 1.30)	0.01
Race (African-American)	0.35 (0.08, 1.51)	0.16

Model with APACHE II calculated two days prior to culture

Variable	**Adjusted OR (95%CI)**	**p value**
FQ-resistant infection	1.38 (0.26, 7.42)	0.71
APACHE II score	1.18 (1.06, 1.32)	0.003
Race (African-American)	0.29 (0.06, 1.37)	0.12

59 Attributable Mortality of Infections Acquired in Intensive Care Units (ICUs)

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Objective: To estimated the attributable mortality proportion (AMP) of ICU-acquired infection (ICU-AI).

Patients and Setting: Data from a surveillance network of ICU-AI in 11 ICUs of the Hospices Civils of Lyon, France, between 1995 and 2003 were analyzed

Design: A matched (1:1), nested case-control study was designed. Patients deceased before ICU discharge were defined as cases (C) and survivors as controls (c). We analyzed pulmonary-acquired infections (P-AI), central venous catheter colonisation (Col-CVC), urinary-acquired infections (U-AI) and bacteraemia (B-AI). Only the first infection by site was considered.

Methods: AMP was calculated according to Miettinen (1974) adapted by Kuritz and Landis(1987): AMP = $P_{(E)}$ x [(OR - 1 / OR]. Where $P_{(E)}$ is the prevalence of the cases exposed to ICU-AI and [(OR-1) /OR] is the etiologic fraction of attributable risk for the cases to be exposed at least once to ICU-AI. Analysis was carried out on the discordant pairs and with multivariate conditional logistical regression.

Results: 1316 matched pairs were constituted. No difference existed for the matched variables except for the severity illness score using the Simplified Acute Physiology Score (SAPS II) (C = 46.9 ±17.1 / c = 44.3 ±16.0; $p<0.001$). Comparisons between patients exposed or not to at least one ICU-AI did not show significant differences for all variables excepted length of stay ($p<0.001$). The Table shows the calculated AMP by site and number of infections. Only P-AI and B-AI showed a modest effect on the survival likelihood.

Conclusions: In this very large population-based study, the attributable mortality of ICU-AI was small after careful matching and adjustment for confounding. Previous studies may have overestimated the impact of ICU-AI.

Table's Legend: [*] Conditional logistic regression adjusted on SAPS II score (continuous data), ICU length of stay (≤6 days, >6 days), and patient's origin (home, short term stay unit, average and long stays unit, other ICU). [†] At least one time infection for each of the four sites. [‡] Adjusted Odd-Ratio. [§] Confidence interval with 95%. [#] p-value for McNemar's test. [**] Exposure prevalence among the cases. [††] Adjusted proportions of attributable mortality.

Table. Adjusted* Attributable Mortality Proportions (AMP) of ICU-AI from Data to N=11 ICUs

ICUs-AI exposure[†]	OR_a[‡]	95% CI[§]	*p*[#]	$P_{(E)}$[**]	AMP_a[††]	95% CI[#]
P-AI	2.51	[1.68-3.76]	<.0001	10.9%	6.6%	[4.4% - 8.0%]
Col-CVC	1.21	[0.77-1.90]	.4	6.7%	1.2%	[-2.0% - 3.2%]
U-AI	0.71	[0.45-1.11]	.13	4.4%	-1.8%	[-5.4% - 0.4%]
B-AI	2.41	[1.05-5.54]	.04	2.7%	1.6%	[0.1% - 2.2%]
≥ 2 sites	1.65	[1.17-2.34]	.005	13.0%	5.1%	[1.9% - 7.4%]

60 Computerization of Infection Control in Japan

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Background: Hard-to-cure or incurable nosocomial infections caused by multi-drug-resistant and highly resistant strains are an emerging problem. The pace of antibacterial drug development has decreased significantly since the late 80's and we may lack the antibacterial agents necessary to fight against drug resistant bacteria in the next decade. An aging society restricts medical and welfare resources, so we need more effective and efficient measures for infection control.

Objective: To show that both precision and efficiency in infection control are achievable with computer systems based on proper standardization and algorithms.

Methods: We developed three computerized systems, 1) a national surveillance system (JANIS (the

Japanese Nosocomial Infection Surveillance System)Clinical Laboratory Subdivision; JCLS), 2) a hospital infection control system for large hospitals (National University Infection Control System; NUICS), and 3) a hospital infection control system for smaller hospitals (Small and medium-size Hospital Infection Primary Lookout; SHIPL). These systems utilize a standardized data format (JCLS data format) that includes bacterial test results and patient data, including the bed location.

Results:

More than 200 hospitals nationwide now send monthly data to JCLS. Approximately half of the data sent to JCLS are automatically generated from laboratory computer systems and sent via the Internet. The summarized data are returned via the Internet.

2) NUICS was introduced into six hospitals with six different hospital information systems. It collects data from the hospital information system.

3) SHIPL was introduced into six hospitals with six different outsourcing laboratories. SHIPL obtains data from the laboratories, as most small-to-medium size hospitals in Japan (bed number<200) outsource bacterial tests.

4) Taking advantage of real-time automated data collection, both NUICS and SHIPL can automatically detect an abnormal accumulation of bacterial isolates ward by ward, on a patient basis. Along with other automated data processing functions, the systems have made the early detection of nosocomial infection possible and streamlined infection control activities.

Conclusions:

1) A single standardized data format can be used in computerized national surveillance and hospital infection control systems.

2) Computerized infection control systems with appropriate standardization and algorithms improve both efficiency and precision.

61 Two Methodological Aspects Concerning Time at Risk and Cox Regression Analysis

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Background/Objective/Methods: When analyzing infection surveillance data collected in Dutch ICU's we were confronted with some methodological aspects which have had little attention or explicit reporting in publications up till now, but which can affect results considerably. We go into these aspects, using examples of our own data.

Results:

Time at risk

The incidence density gives the incidence per time period for a given number of people. The time period includes the time a person is at risk of an event, e.g. an infection. Several recent articles still seem to use total follow up time in calculations of incidence densities. It should be explicitly stated whether time at risk or the total follow up time is used and preference given to the former. Our ventilator-associated pneumonia (VAP) rate per 1000 ventilator days (vd) (including those after VAP occurred) was 19 whereas the rate per 1000 vd (at risk) was 25, to illustrate the difference.

Cox regression and proportional hazard ratios over time

Cox proportional hazards regression, besides logistic regression, is frequently used to analyze incidence data on nosocomial infections. Cox regression assumes proportional hazards: a constant ratio between risks of different categories of a risk factor for the time span of the study. This can be checked by 3 methods: graphically, by a test based on the model residuals, or by investigating the statistical significance of an interaction term with time at risk.

The studies using Cox regression, mentioning checking this assumption and finding that it appeared to be violated with some risk factors did not draw consequences. If duration of follow up is short, interaction with time will not have so much effect, but in most surveillance studies, it makes a large difference whether or not this assumption is properly checked and accounted for. In our study the assumption did not apply to the effect of acute admission on the risk of acquiring a catheter-associated urinary tract infection (CA-UTI). Incorporating an interaction term with time at risk in the model, resulted in the relative risk (RR) of 1.8 (p=0.05) for acute admission and of 0.9 (p=0.002) for the interaction with time. This means that acute admission was initially associated with an increased risk of CA-UTI but that this risk diminished with a 10% per day at risk. Not including this interaction would have lead to a very different RR of 0.9 (n.s.).

Conclusions: Explicit description of the used methods and indicators when publishing data, e.g. incidence densities on nosocomial infections enhances the understanding and comparability of results. Testing the proportional hazards assumption when using Cox regression analysis with an interaction term with time at risk compared to the other two methods has the advantage that appropriate hazard ratio's can still be calculated and the insight in the effect of the risk factor is increased.