Published in final edited form as:

Infect Control Hosp Epidemiol. 2009 May ; 30(5): 479–483. doi:10.1086/597061.

The Role of Matching in Case-Control Studies of Antimicrobial Resistance

Elizabeth Cerceo, MD¹, Ebbing Lautenbach, MD, MPH, MSCE^{1,2,3,4}, Darren Linkin, MD, MSCE^{1,2,3,4}, Warren B. Bilker, PhD^{2,3,4}, and Ingi Lee, MD, MSCE^{1,3,4}

¹ Division of Infectious Diseases, Department of Medicine, of the University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

² Department of Biostatistics and Epidemiology, of the University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

³ Center for Clinical Epidemiology and Biostatistics, of the University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

⁴ Center for Education and Research on Therapeutics, of the University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Abstract

Of 57 case-control studies of antimicrobial resistance, matching was used in 23 (40%). Variables on which matching was done differed substantially across studies. Twelve (52%) justified the use of matching and 9 (39%) noted strengths or limitations of this approach. Analysis accounting for matching was performed only 52% of the time.

Introduction

There is growing concern about antibiotic resistance.^{1, 2} Risk factors for antimicrobial resistance have been studied to guide interventions aimed at decreasing their emergence. These studies often employ a case-control study design and may utilize individual-level matching. Matching can be used to control for confounding and is particularly helpful when sample sizes are small, limiting the number of confounders that can be adjusted for in the analysis, or when there is insufficient overlap between case and control subjects (i.e., sibship).^{3, 4} However, it is unclear how often and why a matched case-control study is performed.

The purpose of this study was to investigate the role of matching in case-control studies evaluating risk factors for antimicrobial resistance. We assessed how often matching is utilized; what variables are matched on; whether authors justify the use of or comment on the strengths or limitations of matching; and how often analysis accounting for matching is performed.

Methods

We reviewed the table of contents of four infectious diseases and five general medicine journals we believed would most likely publish articles evaluating risk factors for antimicrobial resistance: Clinical Infectious Diseases (CID), Emerging Infectious Diseases (EID), Infection

Corresponding author: Ingi Lee, MD, MSCE, Division of Infectious Diseases, Hospital of the University of Pennsylvania, 3400 Spruce Street, 3rd Floor, Silverstein Building, Suite E, Philadelphia, PA 19104, Phone: (215) 615-4724, Fax: (215) 662-7611, ingi.lee@uphs.upenn.edu.

Conflict of Interest: All authors report no conflict of interest relevant to this article.

Control and Hospital Epidemiology (ICHE), American Journal of Infection Control, New England Journal of Medicine, Annals of Internal Medicine, Journal of the American Medical Association, Lancet, and British Medical Journal. All abstracts from 2000 to 2005 were reviewed to identify studies that used a case-control study design to evaluate an antimicrobial-resistant pathogen. Full text manuscripts were then read to identify studies that employed individual-level matching.

Two investigators independently reviewed the literature and assessed articles for inclusion (EC and IL). If opinions differed, two additional investigators evaluated the articles (EL and DL) and consensus was used to arrive at a final decision.

The following data were abstracted for each study: journal, year of publication, country of origin, study setting, number of case and control subjects, matched variables (i.e., age, sex, time at risk, and others); whether the use of matching was justified; whether the strengths or limitations of matching were noted; and whether analysis accounting for matching was used (i.e., McNemars test, sign test, paired t test, or conditional logistic regression).

Descriptive analyses were performed to determine how often matching was used and to describe the matched variables. We used Fisher's exact test to assess if matching differed across journal type (i.e., infectious diseases versus general medicine), the particular journal, or year of publication. Chi-square test for trend was used to evaluate the use of matching over time.

Results

We identified 57 case-control studies in six journals evaluating risk factors for antimicrobial-resistant pathogens. A majority (96%) focused on bacterial pathogens. One study evaluated herpes simplex virus, and none evaluated fungal or mycobacterial pathogens.

Of the case-control studies, 23 (40%) from the following three journals utilized individual-level matching: CID = 14 (61%), ICHE = 6 (26%), and EID = 3 (13%). No general medicine journals contained articles meeting inclusion criteria.

Matching was not significantly associated with the journal type ($p=0.51$), a particular journal ($p=0.15$), or year of publication ($p=0.93$). There was no trend in the use matching over time ($p=0.72$).

The most commonly investigated pathogens were: methicillin resistant *Staphylococcus aureus* = 6 (26%), vancomycin resistant *Enterococcus* species = 5 (22%), resistant *Pseudomonas aeruginosa* = 4 (17%), and extended spectrum beta lactamase *Escherichia coli* or *Klebsiella pneumoniae* = 4 (17%). Only two studies were conducted outside the hospital setting.^{5, 6} Although most employed a 1:1 ratio of cases to controls [9 (39%)], several studies used more than one control for each case subject or multiple control groups. Most studies matched on more than one variable [19 (83%)]. The most commonly matched variables were: hospital ward = 11 (48%), date of admission = 8 (35%), time at risk = 8 (35%), age = 6 (26%), and sex = 5 (22%).

Twelve (52%) articles used statistical tests accounting for matching. Twelve articles (52%) justified the use of matching and 9 (39%) discussed the strengths or limitations of matching. Controlling for confounding was the primary justification and primary strength given.^{3, 4}

Discussion

In the nine journals we reviewed, individual-level matching was used in 40% of case-control studies evaluating risk factors for antimicrobial-resistant pathogens. Most matched on more

than one variable, and these variables differed substantially across studies. Half the articles justified the use of matching and 39% acknowledged the strengths or limitations of matching. Only 52% used statistical tests accounting for matching.

A majority of the studies matched on more than one variable. Falagas and colleagues similarly reported that 76% of matched case-control studies evaluating post-operative infections used more than one matched variable.⁷ In their study, age was most commonly matched variable, followed by surgical procedure, gender, time at risk, and date of operation.⁷ Although age and sex have traditionally been the variables most often used for matching,⁴ we found that hospital ward, date of admission, and time at risk, were more commonly used.

Half the studies justified the use of matching and 39% commented on the strengths or limitations. Most reported that matching was used to control for confounding. The effect of potential confounders can be limited using several methods, including restriction, randomization, matching, or using stratified or multivariable analysis. Matching can be particularly helpful in studies with small sample sizes, where the number of patients may limit the number of confounders that can be adjusted for, or in studies where there may be insufficient overlap.^{3, 4} There are, however, limitations of matching. It can be logistically difficult to identify control patients, particularly if more than one matched variable is used; the matched variable cannot be assessed as a potential risk factor; and if case and control subjects are matched on variables related to the exposure, overmatching can occur.⁴ No articles commented on why matching was used over these other strategies.

Our study reported that only 52% of the studies used matched analysis. If matching is used in the study design, it is important to also use biostatistical tests accounting for matching in the analysis (i.e. McNemars test, sign test, paired t test, or conditional logistic regression). If these tests are not utilized, the benefits of matching done in the design of the study are lost (i.e., potential confounders are not controlled for).^{3, 4}

There are several limitations of our study. We selected a representative sample rather than surveying all infectious diseases and general medicine journals. We believed the selected journals would most likely publish articles evaluating risk factors for antimicrobial resistance. Secondly, data abstraction was limited to the information in these articles. Authors may have been able to justify the use of or comment in further detail on the strengths and limitations of matching if contacted directly.

Matching can be used in case-control studies to adjust for potential confounders. However, matching has important limitations and other alternative methods are available to control for confounding. To better understand the role of matching in case-control studies evaluating risk factors for antimicrobial-resistant pathogens, it would be informative for future studies to justify why matching is being utilized over other available methods. Lastly, it is important for investigators that utilize matching in the study design to then account for matching in the analysis.

Acknowledgments

Financial Support: This work was supported by the Institutional National Research Service Award (T32 AI055435) (I.L.) and by the Mentored Patient Oriented Research Career Development Award (K23-AI-060887) of the NIH from the National Institute of Allergy and Infectious Diseases (D.R.L.).

References

1. Struelens M. The epidemiology of antimicrobial resistance in hospital acquired infections: problems and possible solutions. *British Medical Journal* 1998;317:652–654. [PubMed: 9727997]

2. Gold H, Moellering R. Antimicrobial-Drug Resistance. The New England Journal of Medicine 1996;335:1445–1453. [PubMed: 8875923]
3. Hennekens, C.; Buring, J. Epidemiology in Medicine. Vol. 1. Mayrent, S., editor. Philadelphia: Lippincott, Williams, and Wilkins; 1987. p. 287-323.
4. Woodward, M. Epidemiology: study design and data analysis. Boca Raton: Chapman and Hall/CRC; 2005. p. 273-334.
5. Malvy D, Treilhaud M, Bouee S, et al. A retrospective, case-control study of acyclovir resistance in herpes simplex virus. Clinical Infectious Diseases 2005;41:320–326. [PubMed: 16007528]
6. Lee N, Taylor M, Bancroft E, et al. Risk factors for community-associated methicillin-resistant *Staphylococcus aureus* skin infections among HIV-positive men who have sex with men. Clinical Infectious Diseases 2005;40:1529–1534. [PubMed: 15844078]
7. Falagas M, Mourtzoukou E, Ntziora F, Peppas G, Rafailidis P. Matching criteria in case-control studies on postoperative infections. Journal of Hospital Infection 2008;69:101–113. [PubMed: 18329136]
8. Soriano A, Martinez J, Mensa J, et al. Pathogenic significance of methicillin resistance for patients with *Staphylococcus aureus* bacteremia. Clinical Infectious Diseases 2000;30:368–373. [PubMed: 10671343]
9. Vasquez J, Walker E, Franzus B, Overbay B, Reagan D, Sarubbi F. The epidemiology of mupirocin resistance among methicillin-resistant *Staphylococcus aureus* at a veterans' affairs hospital. Infection Control and Hospital Epidemiology 2000;21:459–464. [PubMed: 10926396]
10. Byers K, Anglim A, Anneski C, et al. A hospital epidemic of vancomycin-resistant *Enterococcus*: risk factors and control. Infection Control and Hospital Epidemiology 2001;22:140–147. [PubMed: 11310691]
11. Ho P, Tse W, Tsang K, et al. Risk factors for acquisition of levofloxacin-resistant *Streptococcus pneumoniae*: a case-control study. Clinical Infectious Diseases 2001;32:701–707. [PubMed: 11229837]
12. Lautenbach E, Patel J, Bilker W, Edelstein P, Fishman N. Extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*: risk factors for infection and impact of resistance on outcomes. Clinical Infectious Diseases 2001;32:1162–1171. [PubMed: 11283805]
13. Moroney J, Fiore A, Harrison L, et al. Clinical outcomes of bacteremic pneumococcal pneumonia in the era of antibiotic resistance. Clinical Infectious Diseases 2001;33:797–805. [PubMed: 11512085]
14. Tacconelli E, Tumbarello M, de Gaetano Donati K, et al. Glycopeptide resistance among coagulase-negative *Staphylococci* that cause bacteremia: epidemiological and clinical findings from a case-control study. Clinical Infectious Diseases 2001;33:1628–1635. [PubMed: 11595984]
15. Carmeli Y, Eliopoulos G, Samore M. Antecedent treatment with different antibiotic agents as a risk factor for vancomycin-resistant *Enterococcus*. Emerging Infectious Diseases 2002;8:802–807. [PubMed: 12141965]
16. Cetinkaya Y, Falk P, Mayhall C. Effect of gastrointestinal bleeding and oral medications on acquisition of vancomycin-resistant *Enterococcus faecium* in hospitalized patients. Clinical Infectious Diseases 2002;35:935–942. [PubMed: 12355380]
17. Harris A, Karchmer T, Carmeli Y, Samore M. Methodological principles of case-control studies that analyzed risk factors for antibiotic resistance: a systematic review. Clinical Infectious Diseases 2001;32:1055–61. [PubMed: 11264034]
18. Lodise T, McKinnon P, Tam V, Rybak M. Clinical outcomes for patients with bacteremia caused by vancomycin-resistant *Enterococcus* in a level 1 trauma center. Clinical Infectious Diseases 2002;34:922–929. [PubMed: 11880957]
19. Lonks J, Garau J, Gomez L, et al. Failure of macrolide antibiotic treatment in patients with bacteremia due to erythromycin-resistant *Streptococcus pneumoniae*. Clinical Infectious Diseases 2002;35:556–564. [PubMed: 12173129]
20. Hirakata Y, Yamaguchi T, Nakano M, et al. Clinical and bacteriological characteristics of IMP-type metallo-beta-lactamase-producing *Pseudomonas aeruginosa*. Clinical Infectious Diseases 2003;37:26–32. [PubMed: 12830405]
21. Jernigan J, Pullen A, Flowers L, Bell M, Jarvis W. Colonization with methicillin-resistant *Staphylococcus aureus* at the time of hospital admission. Infection Control and Hospital Epidemiology 2003;24:409–414. [PubMed: 12828316]

22. Kang C, Kim S, Kim D, et al. Risk factors for and clinical outcomes of bloodstream infections caused by extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae*. *Infection Control and Hospital Epidemiology* 2004;25:860–867. [PubMed: 15518030]
23. Paramythiotou E, Lucet J, Timsit J, et al. Acquisition of multidrug-resistant *Pseudomonas aeruginosa* in patients in intensive care units: role of antibiotics with antipseudomonal activity. *Clinical Infectious Diseases* 2004;38:670–677. [PubMed: 14986251]
24. Schwaber M, Cosgrove S, Gold H, Kaye K, Carmeli Y. Fluoroquinolones protective against cephalosporin resistance in gram-negative nosocomial pathogens. *Emerging Infectious Diseases* 2004;10:94–99. [PubMed: 15078603]
25. Young L, Perdreau-Remington F, Winston L. Clinical, epidemiologic, and molecular evaluation of a clonal outbreak of methicillin-resistant *Staphylococcus aureus* infection. *Clinical Infectious Diseases* 2004;38:1075–1083. [PubMed: 15095210]
26. Abbo A, Navon-Venezia S, Hammer-Muntz O, Krichali T, Siegman-Igra Y, Carmeli Y. Multidrug-resistant *Acinetobacter baumannii*. *Emerging Infectious Diseases* 2005;11:22–29. [PubMed: 15705318]
27. Ernst E, Raley G, Herwaldt L, Diekema D. Importance of control group selection for evaluating antimicrobial use as a risk factor for methicillin-resistant *Staphylococcus aureus* bacteremia. *Infection Control and Hospital Epidemiology* 2005;26:634–637. [PubMed: 16092744]
28. Qavi A, Segal-Maurer S, Mariano N, et al. Increased mortality associated with a clonal outbreak of ceftazidime-resistant *Klebsiella pneumoniae*: a case-control study. *Infection Control and Hospital Epidemiology* 2005;26:63–68. [PubMed: 15693410]

Summary of Matched Case-Control Studies

Table

Lead Author (Year of publication)	Country	Resistant Pathogen	# Cases/ # Controls (Ratio)	Age	Sex	Time at Risk	Other Matched Variables	Justification for Matching	Strengths/ Limitations
Soriano ⁸ (2000)	Spain	MRSA	163/163 (1:1)	No	No	Yes	Co-morbidities, Prognosis	Yes	Yes
Vasquez ⁹ (2000)	USA	Mupirocin-resistant MRSA	96/96 (1:1)	No	Yes	No	Hospital ward, Culture site	No	No
Byers ¹⁰ (2001)	USA	VRE	41/80 (1:2)	No	No	No	Hospital ward, Date of culture	No	No
Ho ¹¹ (2001)	China	Levofloxacin-resistant SP	27/54 (1:2)	No	No	No	Hospital ward, Date of culture	No	No
Lautenbach ¹² (2001)	USA	ESBL EC and KP	33/66 (1:2)	No	No	No	Pathogen (EC vs KP), Culture site, Date of culture	No	No
Moroney ¹³ (2001)	USA	SP with higher cefotaxime MIC	98/157 (1:1.6)	Yes	No	No	Hospital, Co-morbidities	No	No
Tacconelli ¹⁴ (2001)	Italy	Glycopeptide-resistant CNS	20/60 (1:3)	No	No	No	Community versus hospital acquired	No	No
Carneli ¹⁵ (2002)	USA	VRE	233/647 (1:2.8)	No	No	Yes	Hospital ward, Date of admission	Yes	Yes
Cetinkaya ¹⁶ (2002)	USA	VRE	103/186 (1: 1.8)	No	No	No	Hospital ward, Date of admission	Yes	Yes
Harris ¹⁷ (2002)	USA	Imipenem-resistant PA, ampicillin-sulbactam-resistant EC, VRE	120/662 ISPA (1:5.5); 120/770 non-PA (1:6/4) 175:577 ASSEC (1:3.3); 175:934 non-EC (1:5.3) 406/1586 VSE (1:3.9); 406/3134 non-Enterococcus (1:7.7)	No	No	No	Hospital ward, Date of admission	Yes	Yes
Lodise ¹⁸ (2002)	USA	VRE	53/53 (1:1)	Yes	No	Yes	Hospital ward, APACHE II score	Yes	Yes
Lonks ¹⁹ (2002)	Spain & USA	Erythromycin-resistant SP	86/141 (1:1.6)	Yes	Yes	No	Year of culture, Hospital	No	No
Hirakata ²⁰ (2003)	Japan	IMP-type metallo-beta-lactamase producing PA	69/247 (1:3.6)	No	No	No	Year of admission	Yes	No
Jernigan ²¹ (2003)	USA	MRSA	26/78 (1:3)	No	No	No	Date of admission	No	No
Kang ²² (2004)	Korea	ESBL KP	60/60 (1:1)	Yes	Yes	No	Hospital ward, Community versus hospital acquired	No	No
Paramythiotou ²³ (2004)	France	MDR PA	34/34 (1:1)	No	No	Yes	Date of admission, SAPS II	Yes	No
Schwaber ²⁴ (2004)	USA	Cephalosporin- resistant Gram Negative Nosocomial Pathogens Genotype A1 MRSA	282/562 (1:2)	No	No	Yes	---	Yes	No
Young ²⁵ (2004)	USA	MDR <i>Acinetobacter</i>	41/99 non-genotype A1 MRSA (1:2.4); 41/41 non-MRSA (1:1)	No	No	Yes	Date of admission	Yes	Yes
Abbo ²⁶ (2005)	Israel	MRSA	118/118 (1:1)	Yes	Yes	Yes	Hospital ward, Month of admission	Yes	No
Ernst ²⁷ (2005)	USA	MRSA	21/21 MSSA (1:1)	No	No	No	Hospital ward	No	No
Lee ⁶ (2005)	USA	MRSA	21/21 non-SA (1:1)	No	Yes	No	Physician, Clinic, Week of appointment date	No	No
Malvy ⁵ (2005)	France	Acyclovir-resistant HSV	23/46 (1:2)	No	No	No	Hospital, Co-morbidities	Yes	Yes
Qavi ²⁸ (2005)	USA	Ceftazadime-resistant KP	14/14 (1:1)	Yes	Yes	No	Hospital ward	Yes	Yes

Note. - ESBL = extended spectrum beta-lactamase; MDR = multi-drug resistant; SA = *Staphylococcus aureus*; MRSA/MSSA = methicillin-resistant/sensitive *Staphylococcus aureus*; VRE = vancomycin-resistant *Enterococcus*; EC = *Escherichia coli*; ASSEC = ampicillin-sulbactam sensitive *Escherichia coli*; KP = *Klebsiella pneumoniae*; HSV = herpes simplex virus; SP = *Streptococcus pneumoniae*; PA = *Pseudomonas aeruginosa*; IRPA/ISPA = imipenem-resistant/sensitive *Pseudomonas aeruginosa*; CNS = coagulase negative *Staphylococcus*; SAPS = Simplified Acute Physiology Score II; APACHE = Acute Physiology and Chronic Health Evaluation; MIC = minimum inhibitory concentration.