HHS Public Access

Author manuscript

Ann Epidemiol. Author manuscript; available in PMC 2017 November 01.

Published in final edited form as:

Ann Epidemiol. 2016 November ; 26(11): 810–815. doi:10.1016/j.annepidem.2016.09.007.

Examining the Relationship Between Multidrug-Resistant Organism Acquisition and Exposure to Antimicrobials in Long-term Care Populations: A Review

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Abstract

Purpose—Methodological approaches to examining the association between antimicrobial exposure and multidrug resistant organism (MDRO) acquisition are complex. This report's objectives are to review approaches used in and findings of prior studies in the long-term care setting, illustrate how these challenges were addressed in a recently completed large prospective study, and discuss strategies for future studies.

Methods—Key design and analytic approaches used in studies conducted since 2000 examining the association between antimicrobial exposure and MDRO acquisition in the long-term care setting were reviewed. The Study of Pathogen Resistance and Exposure to Antimicrobials in Dementia (SPREAD) in nursing home residents in Boston from 2009 to 2014 is used to illustrate how to approach these challenges.

Results—Prior investigations reporting the association between antimicrobial exposure and MDRO acquisition vary considerably in their approaches. In SPREAD, grouped-time hazard models with complementary log-log link function were used to model acquisition accounting for clustering within facilities using generalized estimating equations and including all days of exposure prior to acquisition.

Conclusions—Future studies in these populations should make use of all available acquisition status data, incorporate the timing of antimicrobial exposure relative to acquisition, and collect detailed covariate information that facilitates examining confounding by indication.

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Keywords

Antimicrobial drug resistance; long-term care; hazard models; antimicrobial exposure

INTRODUCTION

The emergence of multidrug-resistant organisms (MDROs) is a growing public health concern, particularly in the long-term care setting (1) as reflected in the current focus of major US public health initiatives (2). Thus, rigorous epidemiologic research that furthers knowledge on how best to reduce the threat of MDROs has important clinical and public health implications.

Several studies have examined the association between exposure to antimicrobials and MDRO acquisition in the long-term care setting. (3-15) However, their varied designs and analytic approaches limit their interpretability and comparability. Key methodological challenges include: defining exposure, timing and definition of acquisition, selecting a comparison group, and other considerations such as competing risks and clustering within facilities. A prior report that reviewed such methodological challenges among studies conducted prior to 2013 (16), did not focus on long-term care facilities. Some issues pertinent to analyses in this setting were mentioned only superficially (e.g., clustering within facilities) or were not discussed (e.g., competing risk of death). In addition, analytic approaches that maximize the use of data collected in cohort studies were not described.

This report specifically focuses on methodological challenges related to measuring and examining the association between antimicrobial exposure and MDRO acquisition in long-term care facilities. We summarize key prior studies in this setting (Table 1), and provide a direct illustration of how these considerations were applied in The Study of Pathogen Resistance and Exposure to Antimicrobials in Dementia (SPREAD) (14,17-18), the largest prospective study to date examining antimicrobial exposure and MDRO acquisition in long-term care facilities. The study design and main results of the SPREAD study have been described elsewhere (14,17). Briefly, SPREAD was a prospective cohort study conducted in 35 Boston-area nursing homes that examined antimicrobial exposure among 362 nursing home residents with advanced dementia and its association with MDRO acquisition. Each resident was followed for up to 12 months. Research nurses abstracted data describing antimicrobial use (specific agent, dates of administration) for each resident over that time period from the medical administration records. At baseline and quarterly thereafter, research nurses also collected rectal and nasal swabs to assess colonization with the following multidrug-resistant organisms: methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *enterococci*, and multidrug-resistant gram-negative bacteria. Colonization was defined as recovery of a MDRO at either the rectum or nares. Given that SPREAD was the largest and most rigorously conducted longitudinal study of antimicrobial use in long-term care facilities to date, a basic tenet of the analytic approach was to maximize the use of the rich data collected.

Table 1 summarizes key studies of antimicrobial resistance and acquisition of resistant organisms conducted since 2000 in the long-term care setting.

DEFINING ANTIMICROBIAL EXPOSURE

Antimicrobial exposure data are generally available from medication administration records or pharmacy databases such that ascertainment bias is minimal. However, as there is no standardized approach for the selection of antimicrobial exposure thresholds or durations, these measures vary considerably among studies. The most common method dichotomizes exposure at a specific threshold over a time period, such as any versus no antimicrobial use during the prior 30 days (3,6,7,9,10,12,13). Another common approach expresses exposure as the cumulative number of days patients are on antimicrobials. To account for variable observation periods, this measure is often standardized to days of therapy per 1,000 patient-days (i.e., days of therapy is divided by the total number of days the patient is followed in the study, multiplied by 1,000) (19). In using this approach, regardless of standardization for follow-up time, a decision must be made whether to count multiple antimicrobial agents used in a single day as either 1 or more days of therapy. For example, if 2 agents are taken on a single day, this could either be counted as 1 or 2 days of therapy. Sensitivity analyses may be helpful in understanding the relationship between exposure and acquisition, for example to determine if there is a threshold effect or a linear relationship. Ultimately, the operationalization should seek to retain as much of the detailed exposure information collected as possible.

In SPREAD antimicrobial exposure was considered as a time-varying variable to preserve information about antimicrobial exposure relative to acquisition status. While antimicrobial exposure was available for the 30 days prior to enrollment (baseline), we considered only antimicrobial exposure data captured as part of the infection modules collected monthly beginning with baseline. Antimicrobial exposure was calculated cumulatively from baseline until the specific date of the quarterly swabs for a particular interval. For example for the 3-month quarterly assessment, all exposure was calculated between baseline and the 3-month assessment date, while for the 6-month quarterly assessment, all exposure was calculated between baseline and the 6-month assessment date. This exposure variable was measured as days of therapy/1,000 resident-days and its distribution was highly skewed with a large proportion of residents having no exposure. Therefore, we examined the variable in two different formats: (1) any antimicrobials (≥1 day) and (2) log-transformed days of therapy/1,000 resident-days + 1, allowing for residents with no exposure to be included. If multiple antimicrobial therapies were taken on a particular day, this was counted as only a single day of therapy. In separate models, exposure was examined for all antimicrobials and also for specific classes prescribed for more than 10% of episodes, which included quinolones, third/fourth-generation cephalosporins, penicillins, and first-generation cephalosporins. Additionally, sensitivity analyses of exposure prior to acquisition were conducted that explored varying lengths of the exposure window. As the results of the sensitivity analyses were consistent, we included all days of exposure prior to acquisition captured during the study.

TIMING OF MDRO ACQUISITION

While, the exact timing of antimicrobial exposure is attainable from medication administration records, the precise moment a patient acquires a MDRO is impossible to

determine. While time to MDRO acquisition is continuous in nature, MDRO status data can only be collected at specified intervals. Thus, the precision with which the timing of acquisition can be measured is limited by the frequency of microbiological surveillance cultures, e.g., daily, weekly, monthly, or quarterly. In designing a prospective study, this precision must be weighed against practical issues including greater personnel effort, patient burden, and costs. Several prospective studies reviewed in Table 1 collected multiple swabs at varying intervals (6,7,9,10,12,13,15).

As swabs were collected quarterly in SPREAD, acquisition was known only to the nearest quarter. The date of first positive quarterly swab was taken as the time of acquisition.

DEFINING MDRO ACQUISITION

The definition of MDRO acquisition is complex and depends on the pathogen under study, the specific definition of multidrug-resistance, and whether more than one genus or species of multidrug-resistant organism is considered. Studies may define acquisition as the development of new resistance to any MDRO (7,9,15), or to specific species (3-6,8,10-13). Using the most conservative approach, only patients who begin the study free of all multidrug-resistant organisms would be considered at risk for acquiring a MDRO and removed from the at-risk pool as soon as they are positive for any MDRO. A more liberal, but analytically complex, approach would be to allow patients colonized with one type of MDRO to enter the analysis and followed for acquisition of a different MDRO. Given the broad category of MDROs comprises many individual organisms, the possibilities for defining new acquisition with this approach are numerous. Of the 3 studies examining multiple organisms presented in Table 1, 2 used a more liberal approach, (9,15), and 1 used a conservative approach (7).

Another complexity in defining MDRO acquisition is fluctuating colonization status; patients may have a positive swab at the first data collection time point, followed by a negative swab, and return to positive at a third time point. Such fluctuations may reflect either actual gain or loss of a MDRO or variability in laboratory detection methods. Regardless, there is no accepted analytic approach to handling such fluctuations when examining association between antimicrobial exposure and MDRO acquisition. Of the prospective cohort studies reviewed, the majority defined acquisition by a single positive culture (6,7,9,12,13,15), with only 1 study requiring more than 1 positive culture and no subsequent negative cultures (10).

For SPREAD, we hypothesized that the association between antimicrobial exposure with different agents and MDRO acquisition would vary for different organisms; therefore, we modeled 3 separate outcomes: 1. Any MDRO acquisition, 2. multidrug-resistant gram-negative bacteria acquisition, and 3. methicillin-resistant *Staphylococcus aureus* acquisition. Vancomycin-resistant *enterococci* acquisition was not analyzed as an outcome because there were only 3 acquisition cases. For all acquisition analyses, residents were only included if they had a baseline swab, and had survived for at least 3 months such that they had at least one follow-up swab to determine acquisition. Patients who died without acquisition during follow-up after 3 months were censored at the last available quarterly visit.

The most conservative approach was used to define any MDRO acquisition. Residents were only included in this analysis if they were completely free of all multidrug-resistant organisms at baseline, and once a resident acquired any MDRO (methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *enterococci*, and multidrug-resistant gram-negative bacteria), he or she was considered to have experienced the event of interest and thus removed from the "at risk" set. In analyses that specifically focused on multidrug-resistant gram-negative bacteria and methicillin-resistant *Staphylococcus aureus* acquisition, residents had to be free of the specific MDRO of interest at baseline (but could have been colonized with another multidrug-resistant organism), and once that resident acquired the specific MDRO of interest in follow-up, he or she was removed from the at-risk set.

SELECTING A COMPARISON GROUP

There are no controlled trials comparing MDRO acquisition among patients randomly assigned to either receive or not receive antimicrobials in the long term care setting. Most observational studies have utilized a case-control (3,4,8), or nested-case control approach (7) to compare acquisition between exposed and non-exposed groups. Couderc et al. (13) utilized a nested case-case-control study design (20), with 2 separate case-control analyses: the first compared antimicrobial exposure among cases- infected with MDROs (resistant cases) with control-patients without resistant infection caused by the organism of interest, and the second compared cases infected with the susceptible organism of interest (susceptible cases) with control-patients without resistant infection caused by the organism of interest. Other studies utilize a prospective cohort study design to compare acquisition among subjects who do and do not get exposed to antimicrobials with statistical modeling to adjust for potential confounders (6,9,10,12,15).

In the interest of using all available data collected for SPREAD, we chose to model the association between antimicrobial exposure and new MDRO acquisition over 12 months using grouped-time hazard models with complementary log-log link function (21). The resident was the unit of analysis. This method is a natural analogue of Cox proportional hazards regression used when the underlying time to event (acquisition) is continuous but only measured at discrete time points (21), here resident quarters. Thus, all available acquisition status data could be utilized, while recognizing the grouped-time nature of the status data. The resulting inferential statistics are hazard ratios and associated 95% confidence intervals. A similar approach was used for modeling all of the aforementioned MDRO outcomes.

We also conducted a nested 1:1 case-control study as a sensitivity analysis, selecting controls randomly to have follow-up time that matched the timing of acquisition for the cases, as this strategy was used by prior cohort studies (7,13). The magnitude and direction of the resulting associations were similar as the grouped-time hazard models with complementary log-log link function. However, because the case-control approach does not make use of all available data, there was limited power to detect significant associations.

OTHER CONSIDERATIONS

While studies utilizing unmatched and matched case-control designs are routinely analyzed using logistic and conditional logistic regression, respectively, analytic approaches are more varied for prospective cohort studies. Some prospective cohort studies define the outcome as acquisition at any time over the course of follow-up, (6,9,10) which does not make use of all available data when acquisition status is ascertained at multiple time points. Additionally, when antimicrobial exposure data are coarsened to exposure over the entire follow-up period, rather than at intervals prior to each acquisition measure, the relationship between the timing of antimicrobial exposure relative to acquisition is lost. Han et al. (12) and Min et al. (15) used the date of first positive culture as the date of acquisition and time-to-event analyses to model acquisition. However, these studies did not take into consideration the grouped-time nature of the acquisition status data and utilized standard Cox proportional hazards regression analysis and parametric survival analysis, respectively.

Longitudinal analyses may need to consider death as a possible competing risk (22), particularly in older populations. Standard Cox proportional hazards regression is not designed to account for the competing risk of death and can overestimate risk in older populations with high mortality. Thus, methods that account for the competing risk of death are needed to obtain accurate estimates of associations. None of the studies reviewed in Table 1 mention mortality as a potential competing risk, although some studies did report deaths descriptively (5-8,10), or use death for censoring (12,15).

As a final consideration, it is common for patients in these studies to be clustered, either in nursing homes or units within facilities. Many important variables of interest may be correlated within nursing home clusters such as the spread of certain MDROs strains, infection control procedures, and antimicrobial prescribing practices. Thus, analyses must take clustering into account, as many standard statistical approaches assume independence. Studies reviewed that included multiple facilities have either not mentioned taking clustering into consideration (6,9,11,15), or included a facility variable in univariate or multivariable modeling (10,12,13).

Traditional competing risk models cannot be used to estimate cumulative incidence in the presence of time-varying covariates (23). Thus, a full accounting for the competing risk of death was not attempted for SPREAD, as antimicrobial exposure was the primary risk factor of interest and time-varying. However, we did examine the cumulative incidence of acquisition in a competing risks model with no covariates. While the cumulative incidence of acquisition was lower, as expected (22), it was not substantially lower and thus deemed unlikely to alter the result of the findings of the relationship between antimicrobial exposure and MDRO acquisition. Residents were residing in 35 nursing homes; therefore, generalized estimating equations accounted for clustering at the nursing home level (24).

DISCUSSION

There are many complexities to examining the relationship between antimicrobial exposure and MDRO acquisition in long term care populations including defining exposure, timing of

acquisition, defining acquisition, and selecting a comparison group as well as accommodating other considerations such as clustering and competing risks. In this report we summarize these approaches and utilize the SPREAD study to illustrate the use of more advanced statistical methods, such as grouped-time hazard models, to preserve all available acquisition status data, while allowing the timing of antimicrobial exposure relative to acquisition to be more carefully incorporated.

While many existing studies have identified significant associations between antimicrobial exposure and MDRO acquisition (4-8,10-13), several studies have relied on dichotomizations of varying lengths of antimicrobial exposure (5-8,10-11,13) and acquisition (4-8,10-11,13), making it difficult to identify the time course of antimicrobial exposure and subsequent acquisition. In studies that have failed to identify significant associations (3,9,15), multiple risk factors were examined and the studies may have been underpowered specifically to examine antimicrobial exposure.

In all observational studies there is the potential for confounding. Notably, more recently, Datta et al. (25) have found that confounding by indication affects antimicrobial risk factors for some resistant organism acquisition. Schechner et al. (16) describe methods to control for confounding beyond simple covariate adjustment via multilevel analysis that incorporates group-level and individual-level information or through calculation of propensity scores that are used in multivariable modeling. The grouped-time hazard modeling framework provides the flexibility to use either of these approaches. Where feasible we recommend collecting detailed covariate information and utilizing modeling methods that facilitate examining confounding by indication.

Grouped-time hazard models have limitations in accounting for competing risks (e.g., death) as one cannot include time-varying risk factors such as antimicrobial exposure, the primary risk factor of interest in the SPREAD study, and estimate cumulative incidence. Further research is needed to explore alternative methods that allow for modeling time-varying risk factors while accounting for competing risks. The multi-state modeling framework, including the illness-death model, provides potential strategies (23,26-28). These strategies include extending the competing risk model, but this approach is limited by the requirement that the internal covariates be categorical. A second strategy is using landmark analysis to look at cumulative incidence at different subintervals of the entire study follow-up time. This approach allows for internal covariates to be continuous; however, only information at landmark time points is utilized for the internal covariates. Thus, work remains to allow for continuous time-varying risk factors such as antimicrobial exposure to be fully utilized. Additional complexities of antimicrobial exposure that remain to be addressed include the impact of switching agents, interactions between different agents, and dosing. And as many analytic methods rely on status data, other culture data not obtained at pre-specified time points, such as clinical cultures, could be incorporated into analyses.

Finally, biological advances may provide additional advantages for handling these methodological issues. For example, the study of the microbiome may provide information on the mechanisms by which colonization resistance is disrupted (29). Whole genome sequencing (30) may permit more biologically relevant grouping of strains and species for

different pathogens, increasing the comparability and reproducibility of future studies. Further, whole genome sequencing may provide insight into the origins of detected MDROs, allowing distinctions to be made between new MDRO acquisition and previously undetectable colonization.

CONCLUSIONS

Examining the relationship between antimicrobial exposure and MDRO acquisition in long-term care populations is complex. Future studies in these populations should make use of all available acquisition status data, incorporate the timing of antimicrobial exposure relative to acquisition, and collect detailed covariate information that facilitates examining confounding by indication.

Acknowledgments

This work was supported in part by the National Institutes of Health from grants R01AG032982 and K24AG033640 (SLM) from the National Institute on Aging.

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Abbreviations

SPREAD Study of Pathogen Resistance and Exposure to Antimicrobials in Dementia

MDRO Multidrug-resistant organism

Table 1

Review of prior studies that have examined the relationship between antimicrobial exposure and MDRO acquisition in the long-term care setting

Reference No.	First Author, Year	Location	Population	No. of Sites	No. of Participants	Defining Antimicrobial Exposure	Timing of Swabs	Definition of MDRO Acquisition	Study Design	Findings
15	Min, 2015	United States	Nursing home residents	15	111	Dichotomous 30 days prior during follow-up	Monthly until discharge or 12 months	First positive culture; any of Methicillin-resistant *Staphylococcus aureus* , antibiotic-resistant gram negative bacteria, or Vancomycin-resistant enterococci	Prospective cohort	In unadjusted analysis, antibiotic use in the past 30 days significantly associated with time to initial Vancomycin-resistant enterococci acquisition; no significant association in multivariable analysis
13	Couderc, 2014	France	Neurologic patients	4	76 cases; 207 controls; 112 sensitive controls	Dichotomous before admission and after admission	Weekly for 13 weeks	First positive culture; Methicillin-resistant *Staphylococcus aureus*	Nested case-case-control	Fluoroquinolone use significantly associated with Methicillin-resistant *Staphylococcus aureus* acquisition
12	Han, 2014	United States	Long-term care facility residents	3	120	Dichotomous 30 days prior to enrollment and during follow-up (time-varying)	Approximately every two weeks until recovery or up to 12 months or discharge or death	First positive culture; Fluoroquinolone-resistant *E. coli*	Prospective cohort	Amoxicillin-clavulanate use during follow-up significantly associated with Fluoroquinolone-resistant *E. coli* acquisition
11	Olofsson, 2013	Sweden	Nursing home residents	11	268	In the 180 days preceding sampling	Study entry	Positive culture; *E. coli*	Cross-sectional	Antimicrobial use significantly associated with antimicrobial-resistant *E. coli*
10	Stone, 2012	United States	Long-term care facility residents	3	254	Dichotomous in the 3 months before study and during study	Weekly 3 times during first month followed by monthly for 5 months	>1 positive culture and no subsequent negative cultures; Methicillin-resistant *Staphylococcus aureus*	Prospective cohort	Systemic antimicrobial use during study significantly associated with Methicillin-resistant *Staphylococcus aureus* acquisition
9	Fisch, 2012	United States	Skilled nursing facility patients	15	82	Dichotomous any use prior to colonization	Monthly swabs for up to 3 months	Any positive culture; Any new of Methicillin-resistant *Staphylococcus aureus*, Vancomycin-resistant enterococci, Ciprofloxacin-resistant, or Ceftazidime-resistant	Prospective cohort	Antimicrobial use prior to colonization not significantly associated with acquisition
8	Ray, 2010	United States	Long-term acute care hospital patients	1	13 cases; 27 controls	Dichotomous intravenous antibiotics on admission	Routine clinical care and point prevalence surveillance cultures	Any positive culture; *Acinetobacter baumannii*	Case-control	Intravenous antibiotics on admission significantly associated with *Acinetobacter baumannii* acquisition
7	O'Fallon, 2010	United States	Long-term care facility residents	1	29 cases; 29 controls	Dichotomous during interval between baseline culture and follow-up culture	Baseline and every 4 months for up to 12 months of follow-up	Any positive culture; multi-drug resistant gram negative bacteria	Nested case-control	Antimicrobial use during the study significantly associated with multi-drug resistant gram negative bacteria acquisition
6	Manzur, 2010	Spain	Long-term care facility residents	9	196	Dichotomous any exposure during follow-up	Every 6 months for up to 18 months	Any positive culture; Methicillin-resistant *Staphylococcus aureus*	Prospective cohort	Antimicrobial use during follow-up significantly associated with Methicillin-resistant *Staphylococcus aureus* acquisition

Reference No.	First Author, Year	Location	Population	No. of Sites	No. of Participants	Defining Antimicrobial Exposure	Timing of Swabs	Definition of MDRO Acquisition	Study Design	Findings
5	Maslow, 2005	United States	Long-term care facility residents	1	49	Dichotomous use in the 3, 6, 9, and 12 months before study entry	At study entry	Positive culture; Fluoroquinolone-resistant *E. coli*	Cross-sectional	Fluoroquinolone use within the past 12 months significantly associated with Fluoroquinolone-resistant *E. coli* acquisition
4	Nazir, 2004	United States	Long-term care facility residents	1	28 cases matched 4:1 controls to cases	Dichotomous any antimicrobial use and approximate annual days of therapy derived from no. of prescriptions	Routine clinical cultures	Any positive culture; Levofloxacin-resistant *H. influenzae*	Case-control	Any Levofloxacin use significantly associated with Levofloxacin-resistant *H. influenza* acquisition
3	Vasquez, 2000	United States	Acute care patients, long-term care facility residents, and nursing home residents	1	96 cases; 96 controls	Systemic exposure within the previous 30 days	Routine clinical cultures	Any positive culture; Mupirocin-resistant Methicillin-resistant *Staphylococcus aureus*	Case-control	Mupirocin use not significantly associated with Mupirocin-resistant Methicillin-resistant *Staphylococcus aureus* acquisition