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Constitutional Symptoms Trigger Diagnostic Testing Before Antibiotic Prescribing In High-Risk Nursing Home Residents

Angela C. Eke-Usim, MD, MPH,[1] Mary A.M. Rogers, PhD, MS,[2] Kristen E. Gibson, MPH,[3] Christopher Crnich, MD, PhD,[4] and Lona Mody, MD, MSc,[3, 5] on behalf of the Targeted Infection Prevention (TIP) Study Team

[1]University of Michigan School of Public Health, Ann Arbor, MI, [2]Department of Internal Medicine, University of Michigan, Ann Arbor, MI, [3]Division of Geriatric and Palliative Care Medicine, University of Michigan Medical School, Ann Arbor, MI, [4]University of Wisconsin School of Medicine and Public Health, Madison, WI, [5]Geriatrics Research Education and Clinical Center, VA Ann Arbor Healthcare System, Ann Arbor, MI

Corresponding Author 1:

Lona Mody, MD

University of Michigan Medical School

Division of Geriatric and Palliative Care Medicine

300 N. Ingalls Rd., Rm. 905

Ann Arbor, MI 48109

Tel: 734-764-8942

Fax: 734-936-2116

Email: lonamody@umich.edu

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Running Head: Antibiotic Use and Diagnostic Testing in NHs

ABSTRACT

Objectives: To evaluate the use of diagnostic testing prior to treating an infection in nursing home (NH) residents with indwelling devices suspected of having a urinary tract infection (UTI) or pneumonia.

Design: Prospective longitudinal study nested within a randomized trial

Setting: Six NHs in Southeast Michigan

Participants: 162 NH residents with an indwelling urinary catheter and/or enteral feeding tube with 695 follow-up visits [189/695 (28%) visits with an infection].

Measurements: Patient-specific clinical and demographic data—including information on incident infections, antibiotic use, and results of diagnostic tests—were obtained at study enrollment, after 14 days, and monthly thereafter for up to one year.

Results: More than half (100/162 [62%]) of NH residents with indwelling devices had an incident infection requiring antibiotics, with substantial variations between NHs. Besides presence of infection-specific symptoms, change in function was a significant predictor for ordering a chest x-ray to detect pneumonia (*OR* = 1.7; *P* = 0.01). Similarly, change in mentation was a significant predictor for ordering a UA (*OR* = 1.9; *P* = 0.02), chest x-ray (*OR* = 3.3; *P* < 0.01), and blood culture (*OR* = 2.3; *P* = 0.02). Empiric antibiotic use before having laboratory data occurred in 50 of 233 suspected UTI (21.5%) and 16 of 53 (30.2%) suspected pneumonia. Antibiotics were used in 17% of visits without documented clinical or laboratory evidence of infection.

Conclusion: In this study nested within a cluster randomized trial and using data from control sites, we show that constitutional symptoms such as change in function and mentation commonly lead to diagnostic testing with subsequent antibiotic prescribing. Antibiotic use often continues despite negative test results and should be a target for future interventions.

Key Words: antibiotic stewardship; nursing homes; functional decline

INTRODUCTION

In the United States, approximately 1.4 million people reside in over 15,000 nursing homes (NHs).[1] These facilities are crucial to meet the post-acute and long-term care needs of older adults. Multiple comorbidities are common in this population, which contributes to poly-pharmacy, often with the eventual development of antimicrobial resistance and inadvertent side effects.[2-5] NHs are increasingly recognized as reservoirs of multidrug-resistant organisms (MDROs).[5-6]

Antibiotics are one of the most frequently prescribed medications in NHs, with 6% to 10% of residents receiving these medications at any given time[2,7] and 50% to 80% receiving at least one prescription over the course of a year.[8-10] An estimated 25% to 75% of antibiotic prescriptions for NH residents do not meet clinical guidelines for appropriate prescribing.[11-15] Empiric antibiotic treatment (i.e., preemptive administration of antibiotics prior to a definitive diagnosis) is particularly concerning because such use further contributes to overuse and importantly, can be reduced by thoughtful practical interventions.[2-6]

Diagnosis of infections in older NH residents is particularly challenging as they are often frail, have multiple comorbidities, and commonly have atypical clinical presentations.[16,17] For instance, fever may be low or absent in older persons with infections. Moreover, physician visits tend to be infrequent, with many antibiotics prescribed through telephone orders, often by on-call physicians, and initiated without a preceding physical examination or confirmatory diagnostic test.[3,13] Ideally, in the absence of advanced directives from the resident or primary caregiver limiting medical interventions, NH residents with a suspected infection should have appropriate diagnostic laboratory tests performed and the results reviewed by their primary care provider.[18]
While early administration of antibiotics may be prudent in severe cases, most situations can be managed conservatively while awaiting diagnostic test results.

In this study, our aim was to evaluate the use and timing of diagnostic testing prior to initiating an antibiotic regimen in high-risk NH residents with an indwelling urinary catheter and/or enteral feeding tube suspected of having a urinary tract infection (UTI) and/or pneumonia. Presence of these devices doubles the risk of infection and antimicrobial use.[19] We were particularly interested in presenting symptoms that lead to diagnostic testing and subsequent antibiotic prescribing. Understanding these triggers is crucial to designing interventions that can successfully change the behavior of physicians, physician extenders, nurses, and care-providers as well as improve patient outcomes.

METHODS

Study Population and Design

The parent study providing data for this longitudinal cohort was a cluster-randomized intervention trial conducted in 12 community-based NHs located in Southeast Michigan from May 2010 to May 2013.[20] The goal of the parent study was to design, implement, and evaluate the efficacy of a multi-component Targeted Infection Prevention (TIP) Program in reducing MDRO prevalence and infections in high-risk NH residents. The project was approved by the Institutional Review Board of University of Michigan. Data were collected by trained research staff employed by the Division of Geriatric and Palliative Care Medicine at the University of Michigan who had clinical experience in NHs. Residents with an indwelling device, including a feeding tube, an indwelling Foley urinary catheter, or a suprapubic urinary catheter, were eligible for this study. Four hundred and eighteen residents (six control sites, n = 215 and six intervention sites, n = 203) were enrolled in the TIP study over the course of three years. For the current study, we used information from the six control sites in the TIP study. Since prospective data were necessary to track incident infections, residents needed two or more visits to be included in the analysis. Fifty-three residents enrolled at the six NHs had a baseline visit only and were eliminated; this yielded 162 eligible residents with an indwelling device of the 215 persons enrolled.

Participants had a study visit at baseline, after 14 days, and monthly thereafter for a maximum of one year (or until death, discharge, or device discontinuation). Follow-up time for each participant was the time from initial enrollment (day 0) until the last follow-up visit was completed. Clinical and demographic data were obtained at each visit from the source documents at the participating facility or by chart review conducted by trained research staff. We recorded descriptive data at the time of admission and prospectively tracked diagnostic tests and incident infections from the first follow-up visit (day 14) to capture predictors of incident events within the NH.

Diagnostic Tests and Infection Criteria

The diagnostic tests of interest were urinalysis (UA), urinary culture, blood culture, sputum culture, and chest X-ray. We assessed whether any of the diagnostic tests were ordered and/or completed (yes/no) within seven days of antibiotic prescribing by reviewing

clinical documentation. In order to be considered infected, a clinical note in the participant's medical record documenting the type of infection and a corresponding prescription of a systemic antibiotic for more than three days to treat that infection were required. We also collected data on residents who were given systemic antibiotics and had a diagnostic test performed but did not have an infection documented.

Clinical symptoms including acute dysuria, fever (>37.9°C [100°F] or a 1.5°C [2.4°F] increase above baseline temperature), new or worsening urgency, frequency, or incontinence, suprapubic pain, gross hematuria, costovertebral angle (flank) tenderness, rigors, or change in functional status were documented for patients with a diagnosis of a UTI.[21] Change in function was defined as either a clinician note documenting an acute functional decline or a change in functional status score using Lawton and Brody's Physician Self Maintenance Scale (PSMS), with change in PSMS being a dichotomous variable (change present or absent).[22,23] Symptoms including pleuritic chest pain, fever, cough, new or increased sputum production, and change in functional status were recorded for patients with a diagnosis of pneumonia.[21]

Statistical Analyses

Data were analyzed using a longitudinal panel design. Preliminary analyses began with the characterization of study residents (n = 162) with stratification by antibiotic use (ever [n = 100] vs. never [n = 62]). Differences in means were assessed using a two-sample t-test and differences in proportions were assessed using Pearson's chi-squared test. This was followed by an assessment of the variation in infection rates and antibiotic usage across the 6 NH sites. To assess differences in infection rates across sites, a random-effects Poisson model for panel data was used and offset by the natural log of person-days under observation. A similar model was used to assess differences in the rate of antibiotic use.

Diagnostic testing within 7 days prior to (and including the day of) administration of antibiotics was investigated in residents with UTI or pneumonia who had detailed information regarding the timing of tests and dates of antibiotic use (n = 92 residents). Eight residents had missing or incomplete information regarding antibiotic start and/or stop dates and were excluded. These analyses were stratified by whether the diagnostic test yielded a positive or negative result, in order to assess whether antibiotic use was influenced by the types of diagnostic tests as well as the test results. A diagnostic test was considered confirmatory if it was ordered and completed either on the same day as the antibiotic order or within the 7 days preceding the antibiotic order.

Predictors of diagnostic testing were evaluated using multilevel random effects logit

models, with the likelihood function approximated using the adaptive Gauss-Hermite quadrature method. Use of individual diagnostic tests was modeled separately using the following independent variables: (a) demographic data on admission (age, sex, weight, number of comorbidities from Charlson Comorbidity Score); (b) symptoms (fever, chills, dysuria or hematuria, urgency, frequency, suprapubic pain, and/or incontinence for UTI; fever, cough, sputum, mental status change, and/or chest pain for pneumonia); (c) change in the Physical Self-Maintenance Scale (change present or absent).[22] Alpha was set at 0.05, 2-tailed. Data were analyzed using STATA/MP version 13.1 (StataCorp LP, College Station, TX).

RESULTS

Demographic Characteristics

The 162 eligible NH residents with indwelling devices from 6 NH facilities were observed for an average follow-up of 104 (±122) days, with a total of 857 visits overall (including 695 follow-up visits). Seventy-nine (48.8%) residents had an indwelling urinary catheter, 54 (33.3%) residents had a feeding tube, and 29 (17.9%) residents had both. Of the 162 residents, 100 (61.7%) received one or more courses of antibiotics at some time during follow-up (344 prescriptions). Resident characteristics are shown in Table 1. The mean age of residents was 72.2 (±13.5) years, with the majority being male (93 [57%]) and Non-Hispanic white (118 [86%]). The mean Charlson comorbidity score was 2.9 (±2.1) at baseline. The mean age, gender, race, admission weight, number of comorbidities, and physical functioning were similar in residents who were prescribed antibiotics as those who were not. Overall, antibiotic use was more common in residents with a urinary catheter ($P < 0.001$) compared with those who had a feeding tube only and in those who ever had a pressure ulcer ($P < 0.001$).

Table 2 describes the variation in antibiotic use among the 6 NH facilities. The results are given by visits, with each resident having multiple (≥2) visits. Overall, the mean number of visits was 5 (±4) per person. For 27.7% (189/683) of the follow-up visits, a new infection had occurred within the past 30 days, with significant variation in the proportion infected across the 6 NHs (*range* = 13.5% to 40.6%; $P = 0.008$). The rate of new infection per 1000 device-days was 11.7 (Table 2). Importantly, antibiotics were prescribed in 17% of

494 visits without any documentation of the presence or type of infection.

Predictors of Diagnostic Testing

As expected, having at least one clinical symptom of a UTI was strongly predictive of both UA tests (adjusted odds ratio, *aOR* = 5.3; *P* < .001) and urinary culturing (*aOR* = 5.3; *P* < .001). Similarly, having symptoms specific to pneumonia was predictive of both ordering a sputum culture (*aOR* = 17.2; *P* < .001) and a chest X-ray (aOR = 6.5; *P* < .001). Symptoms suggestive of UTI (*aOR* = 2.5; *P* = 0.01) also predicted obtaining blood cultures.

Residents who had a fever (>100ºF or 2.4ºF increase above baseline temperature) were more likely to have a chest x-ray, a sputum culture, and a blood culture compared to residents without a fever (Table 3). Residents who had a change in mental status (new onset delirium or confusion) were more likely to have a UA, a chest x-ray, and a blood culture done compared to residents without a change in mentation. Similarly, residents who had a change in physical functional status were more likely to have a chest x-ray, a sputum culture, and a blood culture compared to residents without a change in function.

Antibiotic Use and Diagnostic Testing for UTI and Pneumonia

Three hundred and forty-four prescriptions were written for indications of pneumonia or UTI in 92 residents. Of these, 38% (*n* = 131) of antibiotic prescriptions were written and/or started before a laboratory test was done; 62% (*n* = 213) were started following a confirmatory diagnostic test consistent with the infection. The average number of antibiotic days for the treatment of a UTI was 7 days (*range* = 1 to 60 days) and for pneumonia was 7.5 days (*range* = 1 to 29 days), based on those residents who had information regarding diagnostic testing and antibiotic use.

Figure 1 displays whether a diagnostic test was obtained in the 7 days prior to the onset of an antibiotic regimen. Physicians did not utilize the most recent diagnostic test(s) prior to prescribing antibiotics in 21.5% of instances in which a UTI was suspected (50/233) and in 30.2% of instances in which pneumonia was suspected (16/53) (Figure 1). Among 233 instances of UTI, a UA was the most commonly performed diagnostic test prior to prescribing an antibiotic (*n* = 161; 69.1%), followed by a urine culture (*n* = 142; 60.9%). In approximately one-third of instances, there was either no request for a UA or the results were not available prior to initiation of treatment for a suspected UTI. Blood cultures were conducted in 18% of instances (*n* = 42) prior to antibiotic prescribing in residents with a suspected UTI. Among 53 instances of treatment for pneumonia, a chest X-ray was the most commonly performed diagnostic test (*n* = 30; 56.4%) prior to prescribing an antibiotic, followed by a sputum culture (*n* = 14; 25.4%).

Figure 2 is a representation of antibiotic use following the review of diagnostic test results. In those observations in which a UTI was identified, a positive UA or urine culture led to antibiotic administration in 89.7% of instances (209/233). The vast majority of antibiotics were discontinued if results of a UA or chest X-ray were negative. However, in 25 (17.6%) urine cultures, antibiotics for a UTI were continued despite negative results. Blood culture results were often negative when residents received antibiotics for either UTI or pneumonia (81.0% and 88.2%, respectively).

DISCUSSION

Empiric antibiotic use among older NH residents is concerning, prompting national calls to redesign infection control and prevention programs in NHs.[3] In this study, we explore predictors of diagnostic testing, variations in antibiotic usage, and the extent to which different diagnostic tests influence decisions concerning antibiotic prescriptions. Along with infection-specific symptoms, a change in function and mentation often trigger diagnostic testing. Additionally, we show that test-guided antibiotic use exceeds empiric prescribing, though antibiotics were initiated without employing diagnostic testing in 21.5% suspected UTIs and in 30.2% suspected pneumonia infections. However, the use of antibiotics in NH residents often continues despite negative laboratory tests for suspected infection. Our results suggest that diagnostic testing should be used more promptly and effectively in order to reduce inappropriate antibiotic use.

Inappropriate antibiotic use leads to poor patient outcomes, including adverse drug events, higher healthcare costs, and antimicrobial resistance.[3,9] While many different criteria are used to judge the appropriateness of antibiotics prescribed, the majority of longitudinal surveillance studies find at least 50% of antibiotic courses to be inappropriate.[11-15] Katz et al[13] found that information derived from laboratory test results or physical examination figured in the antibiotic prescription process approximately 50% of the time, and a survey of more than 200 NH residents in the US noted the presence of localizing signs and symptoms in only 46% of the residents for whom antibiotics were ordered.[15] Also in that study, appropriate cultures were obtained in only 58% of suspected UTIs, and sputum cultures in 3% of suspected lower respiratory tract infections.[15] In our study, antibiotics were used in the past 30 days for 99% of visits in which a UTI or pneumonia occurred (as defined by study criteria) and in 17% of visits in which the resident did not have an infection. More than one-third of antibiotic

prescriptions for UTI or pneumonia were written or started before a laboratory test was done.

Our results also show that a change in function and mentation commonly triggers further diagnostic testing. Professional societies such as the Infectious Disease Society of America emphasize functional assessment as part of the infectious disease evaluation in an older adult.[24] However, although a progressive infection can present as a change in function or mentation , not all of these changes are due to an infection. Further research on minimum differential diagnostic considerations in patients with acute functional and mental status change in hospitals and NHs is urgently needed. In particular, defining the probability of infection when a resident has isolated functional or mental status change has the potential to substantially change physician prescribing practices.

Our study highlights how different diagnostic tests influence decisions concerning antibiotic prescription in NHs. Following review of test results, the prescribing physician or physician extenders must reach a treatment decision, sometimes with incomplete information. While failing to treat an older adult based on a negative test result reduces inappropriate antibiotic use and thus enhance resident safety, frontline providers may have concerns regarding the potential rapid decline if an infection remained untreated. Thus, the benefits of over-treating patients with clinically suspected infections but negative diagnostic tests must be balanced by the contributory development of antibiotic resistance and other adverse events in the larger population as a whole.[25, 26] A growing body of evidence demonstrates that the effectiveness of simple educational interventions, a proactive approach needs to be implemented to curb and eventually eliminate inappropriate antibiotic usage in NHs.[4,20,27-29]

Major strengths of this study are its prospective longitudinal design that involved high-risk residents from multiple free-standing NHs. Data was collected by trained research staff. We acknowledge several limitations as well. We did not collect information on the prescribing clinicians' specialty. Additionally, the focus of this study was NH residents in Southeast Michigan who had an indwelling device and were at a higher potential risk of infection than most residents in NHs; therefore, the results may not be generalizable to all NH residents. Our population is slightly younger and includes more males who have indwelling urinary catheters. It is also important to point out that our analysis of diagnostic testing focuses on those individuals who received antibiotics; our study did not collect information on individuals for whom a test was ordered but no antibiotic was prescribed. This would be an important population to examine in future studies.

In conclusion, we found a relatively high percentage of empiric antibiotic use in NHs in the absence of clinical evidence of infection with substantial variations between NHs.

While the indications of laboratory testing appeared appropriate, the results of laboratory testing did not necessarily inform decision-making regarding antibiotic treatment. Further studies to improve antibiotic stewardship in NHs should address clinical decision-making based on symptomatology and the interpretation of diagnostic test results. Avenues for more rapid, yet accurate, testing may be worth exploration so that antibiotics can be expeditiously targeted to those who would most likely benefit. Such approaches should augment efforts to improve antibiotic stewardship, reduce MDROs, and enhance the quality of life among NH residents.

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Table 1. Characteristics of Residents from 6 TIP[a] study Nursing Homes (n=162)

Resident Characteristic	Antibiotics Prescribed (n=100)	No Antibiotics Prescribed (n=62)	Total (n=162)	P-value
Age, mean (±SD)	73 (±13)	71 (±14)	72 (±14)	0.54
Males, n (%)	61 (61)	32 (52)	93 (57)	0.24
Non-Hispanic white, n (%)	73 (86)	45 (85)	118 (86)	0.87
Weight, lbs, mean (±SD)	180.9 (±64.7)	167.0 (±61.1)	175.4 (±63.5)	0.19
Charlson comorbidity score, mean (±SD)	3.0 (±2.0)	2.8 (±2.2)	2.9 (±2.1)	0.50
Ever had pressure sore, n (%)	65 (65)	18 (29)	83 (51)	<0.001
PSMS, mean (±SD)[b]	22.1 (±3.8)	21.9 (±4.4)	22.0 (±4.0)	0.81

SD = standard deviation; PSMS = physical self-maintenance scale.

[a] Targeted Infection Prevention (TIP) study included residents with indwelling urinary catheters and/or feeding tubes.

[b] PSMS scores range from 6-30, with higher scores reflecting greater dependence.

Table 2. Variation in Antibiotic Utilization among Nursing Homes

	Nursing Home Facility						
Characteristic	I	II	III	IV	V	VI	All
Total number of visits	96	177	100	93	107	122	695
Number (%) visits with ≥1 infection[a]	13 (13.5)	57 (32.4)	20 (21.1)	23 (25.6)	43 (40.6)	33 (27.5)	189 (27.7)
Infection rate (per 1000 device-days)	4.6	16.3	8.9	9.5	16.6	10.5	11.7
Days of antibiotic use with UTI or pneumonia, mean (±SD)	10.5 (±3.2)	10.9 (±6.6)	10.5 (±4.9)	8.5 (±6.2)	13.1 (±6.5)	12.5 (±6.4)	11.3 (±6.2)
Charlson comorbidity score, mean (±SD)[b]	3.3 (±2.6)	3.1 (±2.2)	1.9 (±1.1)	3.0 (±2.8)	2.6 (±1.7)	3.4 (±1.9)	2.9 (±2.1)
NH ownership	Non-Profit	Profit	Profit	Profit	Non-Profit	Profit	

NH = nursing home; UTI = urinary tract infection.

[a] New infection within last 30 days. Infection was unknown at 12 visits.

[b] At first visit.

Table 3. Constitutional Symptoms and Diagnostic Tests.

	Diagnostic test OR (95% CI) p-value				
	Urinalysis	Urine Culture	Chest X-Ray	Sputum Culture	Blood Culture
Fever	1.2 (0.6, 2,2) 0.67	1.1 (0.6, 2.0) 0.86	**4.8 (2.5, 9.0)** **<0.001**	**6.3 (2.0, 19.7)** **0.002**	**26.9 (10.2, 70.6)** **<0.001**
Change in mentation	**1.9 (1.1, 3.1)** **0.02**	1.3 (0.8, 2.2) 0.32	**3.3 (1.9, 5.7)** **<0.001**	0.2 (0.03, 1.8) 0.17	**2.3 (1.2, 4.6)** **0.02**
Change in function	1.4 (1.0, 2.1) 0.07	1.3 (0.9, 1.9) 0.21	**1.7 (1.1, 2.5)** **0.01**	**2.5 (1.4, 4.4)** **0.002**	**2.1 (1.4, 3.2)** **0.001**

OR = odds ratio.

FIGURE LEGENDS

Figure 1. Bar chart showing % of residents who received antimicrobials and had the diagnostic test performed within 7 days of antibiotic prescription for urinary tract infection (UTI) or pneumonia. Physicians did not order any test prior to prescribing antibiotics in 21% of UTIs and 30% of pneumonia. Column labels represent the percentage. Any test = any of the 3 tests listed; X-ray = chest X-ray.

Figure 2. Bar chart showing % of antibiotic use among residents following the review of laboratory test results. The majority of antibiotics were discontinued if results of a urinalysis (UA) or chest X-ray were negative. However, in 25 (18%) urine cultures, antibiotics for a urinary tract infection (UTI) were continued despite negative results. Column labels represent the percentage. X-ray = chest X-ray.

Figure 1.

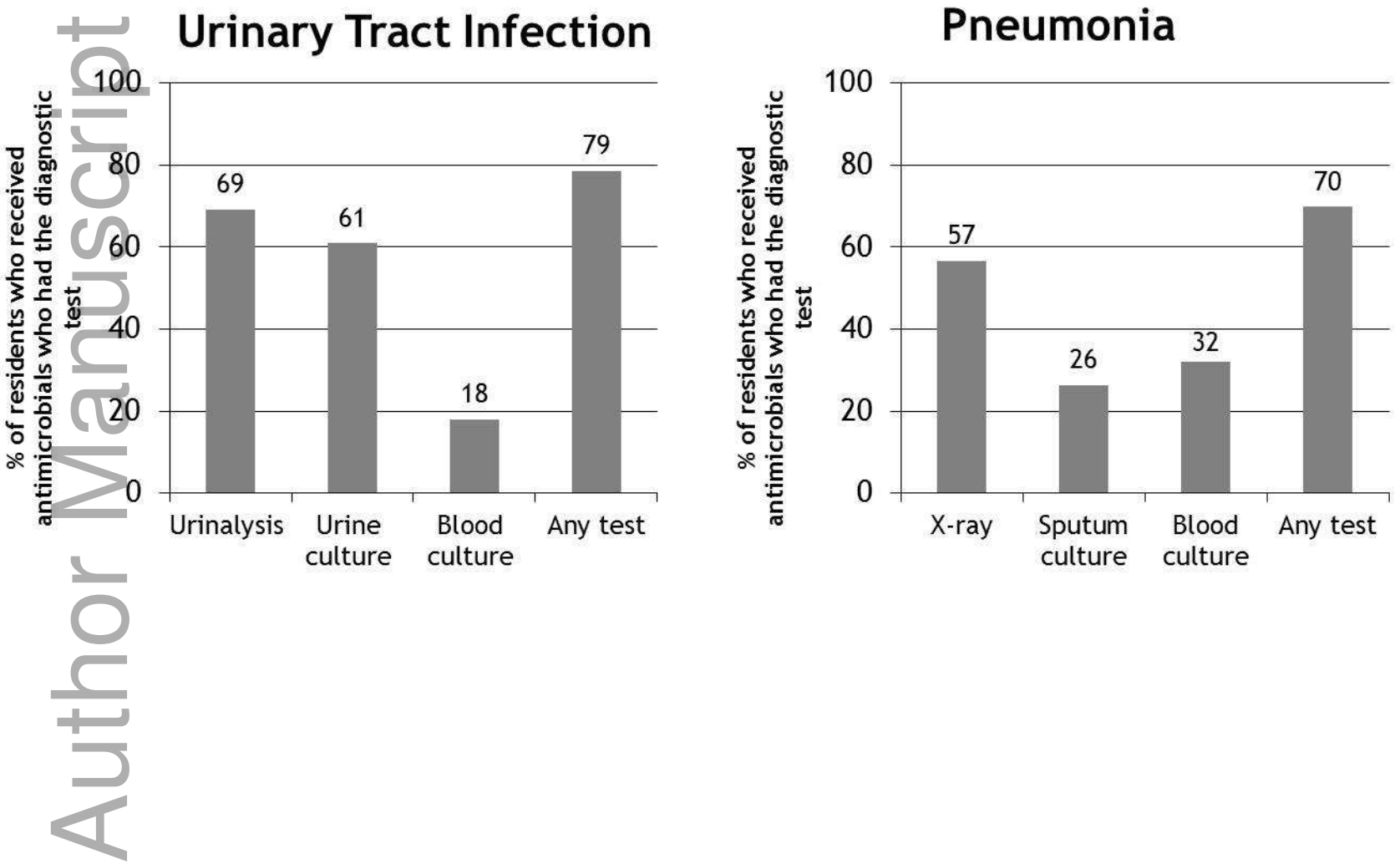

Figure 2.