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Ibrahim Al-Busaidi, MD;[1,2]
Jerome A. Leis, MD, MSc;[1,2,3]
Wayne L. Gold, MD;[1,2]
Allison McGeer, MD, MSc;[1,4]
Ants Toi, MD[5]

Affiliations: 1. Division of Infectious Diseases, Department of Medicine; University of Toronto, Toronto, Ontario, Canada; 2. Department of Medicine, University of Toronto, Toronto, Ontario, Canada; 3. Centre for Quality Improvement and Patient Safety, University of Toronto, Toronto, Ontario, Canada; 4. Division of Medical Microbiology, Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada; 5. Department of Medical Imaging, University of Toronto, Toronto, Ontario, Canada.

Address all correspondence to Ibrahim Al-Busaidi, MD, Division of Infectious Diseases, 200 Elizabeth Street 13EN-213, University Health Network, Toronto, Ontario, Canada M5G 2C4 (ibrahimbusaidi@gmail.com).

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Characteristics of Primary Literature in the Field of Antimicrobial Stewardship, 2000-2013

To the Editor—The spread of drug-resistant pathogens and a lack of novel antimicrobial agents impact human health worldwide. Consequently, antimicrobial stewardship (AS) strategies that conserve the utility of existing antimicrobials and enhance appropriate drug use are of significant importance. Current and widespread interest in AS is reflected by recent governmental statements supporting the expansion of AS initiatives and by a recent white paper from the Society for Healthcare Epidemiology of America that provides guidance for the knowledge and skills required for AS leaders.[1,2] In directing AS efforts, evidence-based interventions are required to ensure the most efficient use of available resources.

A guideline for the development of an institutional program to enhance AS was published in 2007 by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America.[3] Additionally, several reviews have been published on the topic.[4,5] Such publications provide a detailed analysis and perspective of the literature, but opportunity exists to provide a more global perspective on the status of this area of research. The purpose of this letter is to complement existing literature, document trends in practice, elucidate knowledge gaps, and identify future needs by objectively describing characteristics of original AS research from 2000 to 2013.

A structured literature search utilizing PubMed (http://www.ncbi.nlm.nih.gov/pubmed) was performed in August 2014 using the term "antimicrobial stewardship" to identify existing publications within this area of study. Search filters included the following: abstract available, human species, English language, and publication date from January 1, 2000, through December 31, 2013. Search results were exported into a spreadsheet (Excel; Microsoft) and publications were individually assessed. Non-primary literature and publications not investigating an AS strategy were excluded from the analysis. Remaining studies were assessed for the following characteristics: year of publication, journal title, journal profession affiliation(s), author profession(s), location(s) of research, institution type, study focus, and financial data. Journal profession affiliations were determined by reviewing online journal descriptions. The 2007 Infectious Diseases Society of America/ Society for Healthcare Epidemiology of America AS Guideline was used to define and categorize the AS strategy or strategies investigated within each publication.

The literature search identified 305 unique publications, of which 88 (29%) were found to be primary literature investigating an AS strategy. Figure 1 denotes the quantity of AS literature produced annually during the study period. No studies published before 2007 met inclusion criteria, yet the number of included publications gradually increased thereafter. North America produced the largest number of

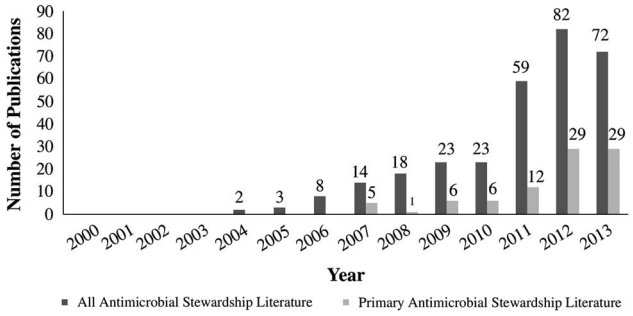

FIGURE 1. Annual publications in the field of "antimicrobial stewardship" from 2000 through 2013.

publications (n = 58), followed by Europe (n = 14), Asia (n = 12), South America (n = 2), Africa (n = 1), and Australia (n = 1). The United States was the country with the most publications (n = 56). In regards to setting, of the 88 studies, 53 (60%) were conducted in a teaching hospital, 23 (26%) were conducted in a community hospital, 4 (5%) were conducted in a long-term care setting, and 8 (10%) did not fall into one of these specific setting categories. Four publications (5%) were specifically focused on pediatric populations.

Thirty-six unique journals published at least 1 included study, and *Infection Control and Hospital Epidemiology* published the most articles (n = 14). The medical (n = 47) and pharmacy (n = 18) disciplines were the most common journal professional affiliations identified. Analysis of author disciplines identified 55 interprofessional collaborations, of which 48 featured at least 1 physician and 1 pharmacist.

All AS core and supplemental elements were found to have been studied, with 55 publications investigating multiple strategies and 33 investigating a single strategy. The most common strategies investigated were guidelines and clinical pathways (n = 29) and prospective audit with intervention and feedback (n = 24). The least common strategies investigated were antimicrobial cycling (n = 3), combination therapy (n = 3), and antimicrobial order forms (n = 1). In regards to which therapies were targeted, 51 studies (58%) addressed antibacterials, 9 (10%) addressed antifungals, 3 (3%) addressed antivirals, and 25 (28%) had no particular focus. In regards to which pathogens were targeted, 35 studies (40%) focused on a specific organism or group of organisms. The most commonly targeted pathogen was *Clostridium difficile* (n = 10 studies).

For economic end points, 31 studies (35%) discussed financial implications, of which 27 (87%) provided objective financial end point data. Cost savings was reported by 24 studies, 2 studies reported a neutral economic impact, and 1 study reported increased costs. For funding, 41 studies (47%) provided a direct funding source, 30 studies (34%) did not provide a funding disclosure, and 17 studies (19%) were stated to be unfunded.

These data show that a large number of journals have interest in AS, interprofessional collaboration within AS research is frequent, funding exists to perform AS-related research, and AS literature has increased precipitously over the past 10 years. However, the availability of primary literature in this area remains limited and many opportunities exist to expand on current knowledge. For example, data show expansion of research is needed within pediatric populations and long-term care locations. Furthermore, several AS strategies are particularly in need of study (eg, antimicrobial order forms).

Study limitations include a search restricted to the English language and query of only 1 database. A more extensive search may have provided additional primary publications. In addition, the term "antimicrobial stewardship" has become mainstream only in the past decade or so. It is possible that AS was simply not mentioned or was identified by alternative means in non-included publications, resulting in an underrepresentation of the literature.

As AS becomes further integrated into healthcare delivery systems, implementation of research initiatives to fill existing knowledge gaps is essential to elucidating the optimal management of potential AS endeavors. Development of an interprofessional journal or journal sections for AS-specific content may soon be warranted.

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Melissa Santibañez, BS;[1]
Melissa V. Veulens, BS;[1]
Tatiana Jenistova;[1]
Laura Aragon, PharmD, BCPS-AQ ID;[2]
Timothy P. Gauthier, PharmD, BCPS-AQ ID[1]

Affiliations: 1. College of Pharmacy, Nova Southeastern University, Fort Lauderdale, Florida; 2. Department of Pharmacy, Jackson Memorial Hospital, Miami, Florida. (Dr. Gauthier is now with the Department of Pharmacy, Miami Veterans Affairs Healthcare System, Miami, Florida. Laura Aragon previously used the name Laura Smith.)

Address correspondence to Timothy P. Gauthier, PharmD, BCPS-AQ ID, Department of Pharmacy, Miami Veterans Affairs Healthcare System, 1201 NW 16th St, Miami, FL 33125 (timothy.gauthier@va.gov).

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Detection of *Mycobacterium abscessus* from Deep Pharyngeal Swabs in Cystic Fibrosis

To the Editor—The prevalence of nontuberculous mycobacteria (NTM) respiratory infection is increasing in cystic fibrosis (CF), particularly with rapidly growing mycobacterial (RGM) species such as *Mycobacterium abscessus*.[1,2] Because NTM infection, and *M. abscessus* in particular, is associated with poor clinical outcomes,[3] regular screening using specialized culture methods for acid-fast bacilli (AFB) on sputum has been recommended, even for stable patients with CF.[1,4] However, these screening methods are difficult to apply in young children who often cannot produce sputum, even with induction. Respiratory samples from these children are typically obtained using deep pharyngeal swabs (also called oropharyngeal or cough swabs), but published studies suggest that this sample may not be appropriate for AFB cultures.[5,6] In fact, the recent SHEA guidelines on infection prevention and control for cystic fibrosis patients specifically recommends against the use of oropharyngeal swabs to screen for these organisms, stating that individuals without clinical features of NTM pulmonary disease who are unable to spontaneously expectorate sputum do not require screening.[1]

Although the prevalence of *M. abscessus* infection is generally low at young ages, infection can occur as early as infancy and can be clinically significant even before school age.[7,8] Furthermore, the use of chronic macrolide therapy with CF is increasing in young children and is being studied in infants (clinicaltrials.gov NCT01270074), but this therapy is contraindicated with NTM respiratory infection due to the potential to induce resistance.[9] Thus, screening methods capable of early detection of these pathogens in young, non-expectorating children could have considerable value.

We recently reported a novel RGM culture method designed to facilitate recovery of rapidly growing mycobacteria such as *M. abscessus* from routine CF bacterial cultures using 14-day incubation of *Burkholderia cepacia* selective agar plates.[10] This study evaluated all respiratory samples from children and adults with CF over a 2-year period and included deep pharyngeal swabs, which allowed us to perform a retrospective analysis to assess the utility of this culture sample method for *M. abscessus* detection (IRB approval 11-0828). Of the 695 patients studied, 311 had at least 1 deep pharyngeal culture obtained during the study period, with a total of 1,708 total deep pharyngeal cultures (average 2.9 ± 1.9 deep pharyngeal cultures annually). As expected, patients who had at least 1 deep pharyngeal culture obtained were younger than those who did not have any deep pharyngeal cultures (9.9 ± 6.6 years vs 27.4 ± 11.8 years, $P < .001$).

Mycobacterium abscessus was recovered using the RGM culture method in 22 of 1,708 (1.2%) deep pharyngeal specimens, compared with 111 of 3,015 (3.7%) other sample types ($P < .001$). To estimate sensitivity, we identified all patients who had ≥3 positive cultures over the study period, which suggests persistent infection. A total of 10 patients who had deep pharyngeal swab cultures met these criteria, and all but 1 were intermittent sputum producers for whom results from sputum cultures were also available. Among these patients, *M. abscessus* was recovered from 18 of 44 RGM cultures of deep pharyngeal samples (40.9%), compared with 52 of 96 RGM sputum cultures (54.2%, $P = .20$). Standard AFB cultures were performed on most sputum samples, and *M. abscessus* was recovered from 57 of 94 of these cultures (57.4%, $P = .099$ vs RGM on deep pharyngeal swabs). Interestingly, while we observed a positive correlation between AFB smear positivity and AFB culture positivity ($R^2 = .78$, $P < .001$), there was no correlation between AFB smear positivity and deep pharyngeal RGM culture positivity ($R^2 = .02$, $P = .65$).

Although AFB cultures of deep pharyngeal swabs were not performed during RGM culture method study, review of data from a separate, longitudinal study[4] identified 11 instances in which AFB cultures were performed on deep pharyngeal swabs from 6 individual patients with persistent NTM infections (≥3 positive cultures). Of 11 AFB cultures from deep pharyngeal swabs, 5 (45.5%) were *M. abscessus* positive, compared with 45 of 69 AFB cultures of sputum from these patients (65.2%, $P = .31$). Recovery of *Mycobacterium avium* complex pathogens was not observed from any deep pharyngeal AFB or RGM cultures.

These findings suggest that *M. abscessus* can be recovered from deep pharyngeal swabs using standard AFB cultures or the newer RGM culture method. Sensitivity appears lower for deep pharyngeal swabs relative to sputum samples, although differences did not reach statistical significance in these small sample sets. The discrepancy between our findings and previous reports may relate to the large size of our study, in which we analyzed 1,708 deep pharyngeal swabs from 311 individual patients, as opposed to 9 swabs from 6 patients[5] or 145 swabs.[6]

Most patients with persistent infection were intermittent sputum producers, and it is possible that patients able to occasionally produce sputum provide higher-quality deep pharyngeal swabs that contributed to our ability to successfully detect *M. abscessus*. Conversely, our clinical experience suggests that sputum quality in these patients is often poor, which may explain

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