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MAJOR ARTICLE

Discordance Among Antibiotic Prescription Guidelines Reflects a Lack of Clear Best Practices

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Background. Antibiotics are among the most frequently administered drugs globally, yet they are often prescribed inappropriately. Guidelines for prescribing are developed by expert committees at international and national levels to form regional standards and by local experts to form hospital guidance documents. Our aim was to assess variability in antibiotic prescription guidelines for both regional standards and individual hospitals.

Methods. A search through 3 publicly accessible databases from February to June 2018 led to a corpus of English language guidance documents from 70 hospitals in 12 countries and regional standards from 7 academic societies.

Results. Guidelines varied markedly in content and structure, reflecting a paucity of rules governing their format. We compared recommendations for 3 common bacterial infections: community-acquired pneumonia, urinary tract infection, and cellulitis. Hospital guidance documents and regional standards frequently disagreed on preferable antibiotic classes for common infections. Where agreement was observed, guidance documents appeared to inherit recommendations from their respective regional standards. Several regional prescribing patterns were identified, including a greater reliance on penicillins over cephalosporins in the United Kingdom and fluoroquinolones in the United States. Regional prescribing patterns could not be explained by antibiotic resistance or costs. Additionally, literature that cited underlying recommendations did not support the magnitude of recommendation differences observed.

Conclusions. The observed discordance among prescription recommendations highlights a lack of evidence for superior treatments, likely resulting from a preponderance of noninferiority trials comparing antibiotics. In response, we make several suggestions for developing guidelines that support best practices of antibiotic stewardship.

Keywords. antibiotics; antimicrobials; stewardship; prescription guidelines.

Antibiotics are vital drugs in modern medicine, and their use is common throughout clinical care. It is estimated that 30% to 50% of antibiotics are prescribed inappropriately [1], as defined by low adherence rates to antibiotic prescription guidelines [2–13]. Prescription guidelines are available at national and regional levels (referred to as regional standards) and, in many instances, in guidance documents at individual hospitals. Regional standards are generated by committees of national and international experts. Hospital guidance documents are typically generated by a committee of local experts. There has been substantial international and national variability reported in treatment recommendations for diseases like pharyngitis [14, 15] and urinary tract infections (UTIs) [16]. However, the full extent to which guidelines vary in their structure, content, and recommendations has yet to be revealed.

In their most basic form, hospital guidance documents outline recommendations for clinical care and practical information underpinning their implementation. These documents are often developed by practitioners involved in hospital Antibiotic Stewardship Programs (ASPs). ASPs have been gradually adopted by health systems worldwide over the past 10 years, although adoption has been slower in countries with less developed public infrastructure [17, 18]. Hospital guidance documents regarding antibiotic use have been required for hospital accreditation in the United States since 2017 [19] and by France and the United Kingdom since 2008 [18, 20–23]. Guidance documents may include clinical care pathway flowcharts, restricted antimicrobial lists, and hospital antibiotic susceptibility data. The Clinical and Laboratory Standards Institute recommends that susceptibility data be reported in guidance documents, but only 9% of US hospitals have been found to adhere to this recommendation [24, 25]. Furthermore, only 30% of hospitals were reported to review their susceptibility data during document construction [26]. These data call into question the evidence contributing to hospitals' empiric therapy recommendations and highlight the lack of standardized approaches

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to document construction. Although the template underlying the original construction of hospital guidance documents is often unknown, it is expected that publicly available guidance documents and regional standards serve as a blueprint for guideline structure and content.

Regional standards have been developed by professional societies, government bodies, and private organizations. In the United States, the Infectious Diseases Society of America (IDSA) publishes guidelines formulated by expert panels. Also based in the United States is the Sanford Guide to Antimicrobial Therapy, which offers general treatment recommendations from an expert panel as a commercial tool. The United Kingdom has 2 prominent government agencies that publish guidelines, sometimes jointly: the National Institute for Health and Care Excellence (NICE) and Public Health England (PHE). In addition, the British Medical Association, a private organization, publishes prescribing directives through its textbook *The British National Formulary* (BNF). On an international level, the World Health Organization (WHO) convenes a Guideline Review Committee responsible for guideline construction. The European Society of Clinical Microbiology and Infectious Disease (ESCMID) is a nonprofit society that also publishes international guidelines on infectious diseases. Recommendations within the various regional standards are carefully researched and debated to inform their respective jurisdictions on best practices using methods that have been developed by institutions such as the National Academy of Medicine, NICE, and WHO [27]. Regional standards may serve as a starting point for prescription recommendations contained in hospital guidance documents; however, the extent to which hospitals adhere to regional standards is unclear.

In an effort to gauge the landscape of publicly accessible English guidelines, we assessed hospital-based antibiotic prescription guidance documents and regional standards for their structure, content, and prescription recommendations. We reviewed hospital guidance documents for adherence to regional standards. Finally, we analyzed the bases for recommendations in hospital guidance documents and regional standards, which resulted in a set of suggestions for the construction of future guidelines supporting best practices and evidence-based prescribing.

METHODS

Antibiotic Prescription Guidance Document Corpus

We conducted a directed search of keywords (ie, "antibiotic prescription guidelines") using 3 publicly accessible search engines (Google, Bing, Yahoo) to form a preliminary corpus of 30 hospital guidance documents (Supplementary Figure 1). Our inclusion criteria required guidance documents to be at least 5 pages in length, developed by a hospital to provide directives for >1 clinical indication, and written in English. We excluded documents dedicated toward specialized cases (eg, sepsis or prophylaxis) and those not contained within 1 file (eg, multiple PDFs or web pages). These inclusion/exclusion criteria were established in order to allow for document traceability and equivalency between similar guidance documents in terms of content, publication, and dissemination. MEDLINE was deemed an inapplicable database for our search because hospital guidance documents are not typically published in scholarly journals. From our initial corpus of 30 documents, we compared term frequency distributions to the 33 000 most frequently used English words to identify secondary search terms: "amoxicillin," "antibiotic," "antimicrobial," "aureus," "ceftriaxone," "ciprofloxacin," "clindamycin," "clinical," "days," "dose," "dosing," "doxycycline," "empiric," "gentamicin," "infection," "metronidazole," "MRSA," "patients," "penicillin," "plus," "pneumonia," "prophylaxis," "severe," "should," "therapy," "treatment," "vancomycin." This resulted in 40 additional documents (Supplementary Figure 1).

Hospital guidance documents were grouped into 3 regional categories: United States, United Kingdom, and Other (Supplementary Table 1). No other country had sufficient representation ($n > 5$) within the guidance document corpus to allow for an additional regional category that was appropriately comparable. Regional standards were chosen based on their reference within hospital guidance documents. In some instances, academic societies from different regions publish regional standard documents jointly, namely the 2018 UTI guideline from the IDSA and ESCMID [28]. The WHO recommendations were not published in a single file, and instead had to be accessed from their website. This exception to our exclusion criteria was necessary in order to have a relative regional standard representative for the 7 non-Anglophone countries within the "Other" regional category. All documents were the most recent publication at the time of data analysis (2018). Regional standard document updates published after 2018 were deemed not directly comparable to recommendations within our guidance document corpus, published between 2006 and 2017.

Guideline Structure and Content Analysis

For each hospital guidance document, we recorded publication year, document length, word count, frequency of review, and other notable features (Supplementary Table 1, Supplementary Figure 1). Documents were assessed for being diagnosis-oriented (ie, organized to address medications recommended for particular diagnoses) or medication-oriented (ie, organized to address which diagnoses are appropriate for particular medications).

We examined empiric therapy recommendations for community-acquired pneumonia (CAP), UTI, and cellulitis within diagnosis-oriented guidance documents based on their high frequency in clinical care and our corpus (87.1%, 88.6%, and 90% inclusion in guidance documents, respectively). We

omitted penicillin allergy, complication, and second-line therapy recommendations. CAP recommendations were assessed through CURB-65 score degrees of severity: mild (0–1), moderate (2–3), and severe (4–5) [29]. UTI was assessed as cystitis and pyelonephritis. Severity levels for cellulitis were classified as mild, moderate, and severe, as designated by the guidance documents.

We noted the antibiotic recommended by hospital and standard guidelines for each severity of disease and normalized each hospital's number of recommendations to sum to 1. To examine regional recommendation clustering, we performed principal component analysis (PCA) using the "prcomp" function in R on matrices of binary values signifying whether guidance documents recommended an antibiotic. Hospital recommendations were compared with regional standards through 3 concordance measures: Proportion Match, Perfect Subset Match, and Perfect Match (Supplementary Figure 2). We defined a "match" at 2 levels: whether the recommendation matched the same (i) antibiotic or (ii) antibiotic class. If a hospital guidance document recommended an antibiotic class as a whole and the regional standard recommended a different antibiotic in the same class, this would count as a "match" at the class level but not the antibiotic level.

Proportion Match was the number of hospital recommendations that matched standard recommendations divided by the number of standard recommendations. Perfect Subset Match was a binary value assigned to 1 for hospital recommendations being within standard recommendations, but not necessarily including all standard recommendations. Perfect Match was another binary assignment where 1 signified hospital recommendations exactly matching the standard. The 3 concordance scores were calculated for each hospital's recommendations at both levels of matching and averaged across hospitals within each region to yield aggregate concordance scores.

Investigation of Explanatory Factors for Regional Recommendation Patterns

We explored antibiotic resistance rates, antibiotic costs, and the literature base cited to identify factors explaining hospital and regional standard recommendations (Supplementary Figure 1). In order to examine regional antibiotic resistance, we collected hospital-specific susceptibility data from hospital guidance documents. To further validate hospital susceptibility data findings, we used SENTRY [30] susceptibility data from CAP, UTI, and cellulitis patients in the United States and United Kingdom. We analyzed the most common agents for each diagnosis: *S. pneumoniae* for CAP, *E. coli* for UTI, and *Streptococcus* species and *S. aureus* for cellulitis. Fisher exact tests were used to determine the statistical significance of the number of susceptible organisms in the United States vs the United Kingdom.

Absolute cost quantities for drugs were extracted according to route of administration (by mouth [PO] or intravenous [IV]) from corpus hospital guidance documents. Frequencies of hospitals recommending the cheapest antibiotic were calculated for each indication. Average wholesale price (AWP) prescription drug data were considered as an alternative; however, AWP is reportedly an unreliable and unrepresentative proxy for true cost [31]. Therefore, we decided the cost information reported in a subset of hospital guidance documents was a better proxy for determining whether cost was a driver for hospital antibiotic recommendations. Costs were converted to their 2019 US dollar (USD) equivalent for comparison. We defined cost differentials as the price of the cheapest antibiotic relative to alternative recommendations. We bootstrapped cost matrices to estimate frequencies of hospitals recommending the cheapest antibiotic by chance through performing 1000 random samplings with replacement.

We examined the antibiotic prescribing literature base through assessing studies cited by regional standards for recommendations to determine whether differences could be attributed to conflicting evidence in study conclusions. Citations in the recommendation section of each regional standard were assigned a number and merged when they were cited in multiple standards. Only studies that supported the clinical effectiveness of an antibiotic were included in the final list of citations. We also analyzed 10% of PubMed hits using CAP as a representative diagnosis plus CAP corpus recommendations as queries (eg, "community acquired pneumonia[Title/Abstract] AND ampicillin[Title/Abstract]") to determine whether there was strong evidence for some antibiotics over others. We assessed hits for antibiotic efficacy comparisons and noninferiority findings, as reported within their abstracts.

RESULTS

A search for publicly available prescription guidance documents yielded 70 guidelines: 33 United Kingdom, 19 United States, and 18 Other (Figure 1A; Supplementary Table 1). Guidelines originated from a variety of hospitals (ie, private, public, research, or specialty), ranging from 157 to 2700 beds. Documents were published between 2006 and 2017, with the majority published since 2015 (Figure 1B). UK guidance documents were shorter than those from other regions ($P = 5 \times 10^{-4}$, Wilcoxon 1-sided rank-sum test) (Figure 1C). Revision dates were documented sporadically: 33% (n = 23) included a future review date, and 40% (n = 26) included the duration between reviews. About half (n = 39) of documents included an edition number. Author counts varied from 1 to 73, with an average of 12 authors when listed, although 30% (n = 22) did not acknowledge any authors. Contact lists were present in 60% (n = 42) of guidance documents, and a minority (20%, n = 14) contained cost information. Pediatric recommendations were included in 36% (n = 25) of documents (Figure 1D).

Most hospital guidance documents (77%, n = 54) were diagnosis-oriented, while 8% (n = 6) were medication-oriented

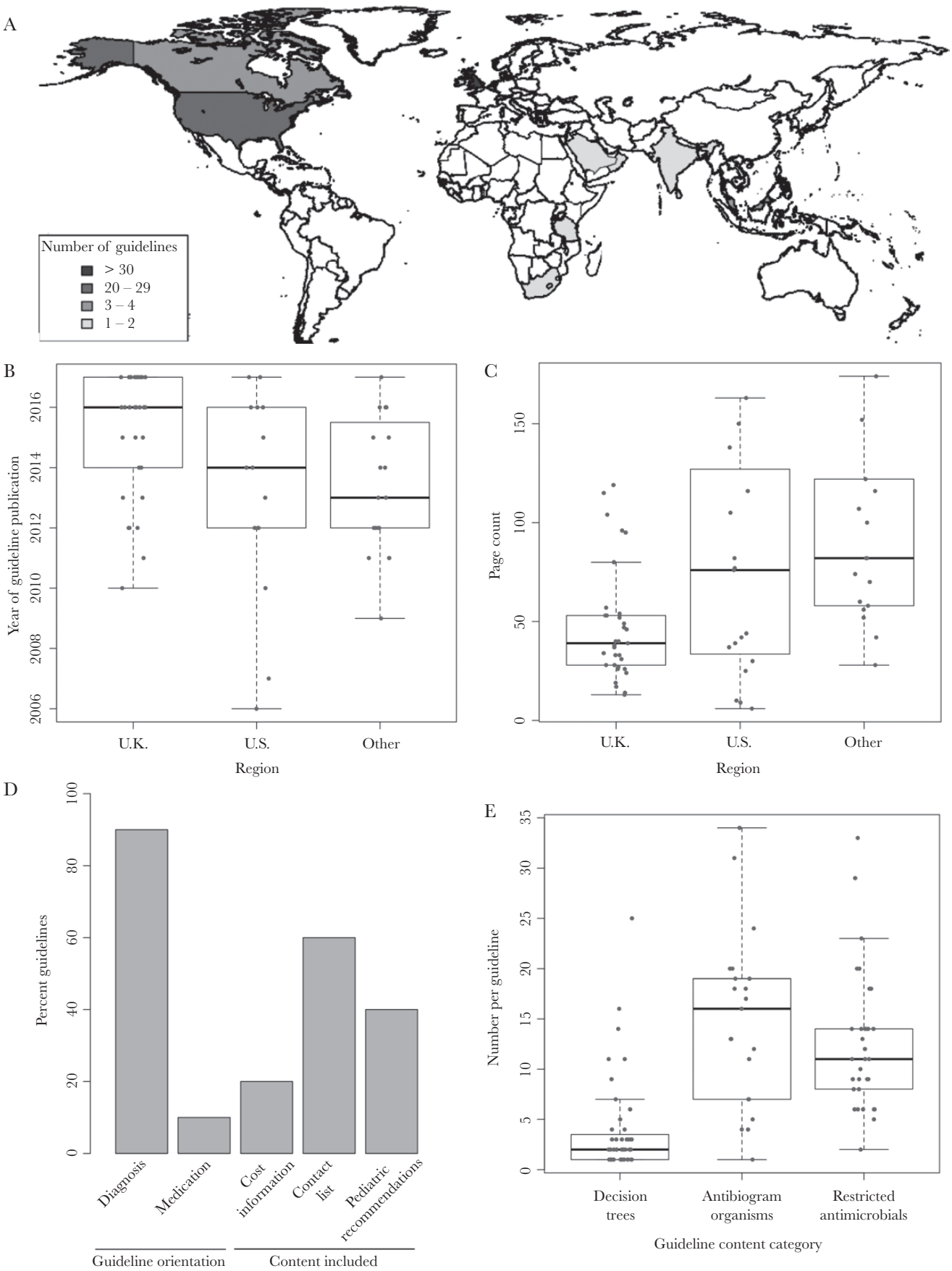

Figure 1. Summary of antibiotic prescription guidance document corpus. A, Distribution of countries of origin for hospital guidance documents included in the corpus. B, Most guidance documents were published between 2012 and 2017. C, Guidance documents ranged in length between 6 and 415 pages. D, Most guidance documents were

(Figure 1E). A majority (60%, n = 42) of guidance documents included at least 1 decision tree. Of these documents, the decision tree number ranged from 1 to 23 per document, with 24% (n = 10) including a tree for treating *Clostridioides difficile* infection and 24% for CAP. A majority of guidance documents (59%, n = 41) mentioned susceptibility data informing recommendations; however, only 30% (n = 21) included such data. Nearly half (47%, n = 33) of guidance documents provided restricted antimicrobials, the most common being meropenem (67%, n = 22) and linezolid (64%, n = 21) (Supplementary Table 2).

Guidelines Make Diverse Recommendations for Common Bacterial Infections

US hospitals generally recommended a macrolide or tetracycline for mild CAP, while UK hospitals recommended a penicillin (Figure 2; Supplementary Figure 3). This discrepancy reflected the recommendation differences between US regional standards (IDSA and Sanford Guide) and others (NICE, BNF, and WHO). For moderate and severe CAP, the majority of US hospitals recommended a cephalosporin plus 1 other drug (eg, ceftriaxone plus azithromycin), whereas UK hospitals recommended a penicillin with 1 or 2 additional drugs.

For cystitis, US hospitals typically recommended trimethoprim/sulfamethoxazole (TMP/SMX) or nitrofurantoin (Figure 2; Supplementary Figure 3). UK hospitals made similar recommendations, with the exception of TMP instead of TMP/SMX, which is unavailable in the United Kingdom. Pyelonephritis recommendations were more variable across hospitals compared with cystitis. Most US hospitals recommended TMP/SMX or a fluoroquinolone. UK recommendations varied among multiple antibiotic classes, reflecting the wide diversity of recommendations made by regional standards at both the class and drug levels (Supplementary Figure 3).

For mild cellulitis, most US hospitals recommended a penicillin or cephalosporin, whereas UK hospitals only recommended penicillins, reflecting their respective regional standards (Figure 2). While US hospitals recommended a variety of antibiotic classes, almost all UK hospitals recommended flucloxacillin, which is unavailable in the United States (Supplementary Figure 3). For moderate cellulitis, IDSA and Sanford were the only standards with published recommendations. About a third (n = 23) of hospitals extended recommendations beyond mild cellulitis. US hospitals recommended penicillin, cephalosporin, or clindamycin for moderate cellulitis, while UK hospitals recommended 1 or 2 penicillins. The IDSA was the only standard with recommendations for severe cellulitis, suggesting piperacillin/tazobactam and vancomycin (Figure 2; Supplementary Figure 3). Hospital recommendations varied dramatically at the drug level for severe cellulitis, furthering a trend toward lower consensus for higher severities.

In terms of concordance scores, recommendations were generally consistent with hospitals' presiding regional standard at the level of antibiotic class (Figure 3). However, on an individual drug basis, hospitals' recommendations often disagreed with each other and their regional standard, resulting in low concordance scores for the US and Other (Supplementary Figure 2). These results are consistent with the notions that regional standards provide guidance largely at the class level and that hospitals select individual agents within a class of drugs. UK hospitals had greater concordance scores to UK standards than US and Other hospitals to their respective standards. Concordance scores for Other hospitals were spread across standards at both the drug and class levels, suggesting that countries within Other might have drawn recommendations from multiple sources. PCA illustrated a significant difference between regional recommendations for CAP, cellulitis, and all diagnoses together, while regional differences were not statistically significant for UTI (Supplementary Figure 4).

Lack of Definitive Evidence Likely Contributes to Variable Recommendations

As most hospitals did not report susceptibility data, we used a combination of hospital and SENTRY data to investigate resistance as a potential explanation for the observed regional differences in US and UK recommendations. That is, cephalosporins and fluoroquinolones were commonly recommended as empiric therapy in the United States, and penicillins were more frequently recommended in the United Kingdom. The SENTRY (Supplementary Table 3) and hospital guidance document (Supplementary Table 4) susceptibility data demonstrated that susceptibility proportions were in accordance with regional recommendation patterns for cellulitis *S. aureus* isolates and CAP but not for cellulitis *Streptococcus* isolates or UTI. For CAP, we found significantly different log odds ratios for greater penicillin susceptibility in the United Kingdom (Supplementary Tables 3 and 4) and greater levofloxacin susceptibility in the United States (Supplementary Table 3), which supported observed regional recommendations. For UTI, significant log odds ratios conveyed greater penicillin plus β-lactamase inhibitor susceptibilities in the United States (Supplementary Table 3), which did not align with regional patterns. For cellulitis, significant log odds ratios exhibited greater cephalosporin susceptibility for US *Streptococcus* isolates and greater cephalosporin and penicillin susceptibility for UK *S. aureus* isolates (Supplementary Table 3). Therefore,

oriented toward providing information according to diagnosis, as opposed to focusing on applications of individual antibiotics (ie, medication orientation). Guidance documents varied in their inclusion of cost information, a contact list, and recommendations for pediatrics. E, Guidance document content reflected the variability in approaches to antibiotic stewardship as conveyed through the number of guideline content entities contained within documents. Guidance documents that contained 0 of a content entity were omitted.

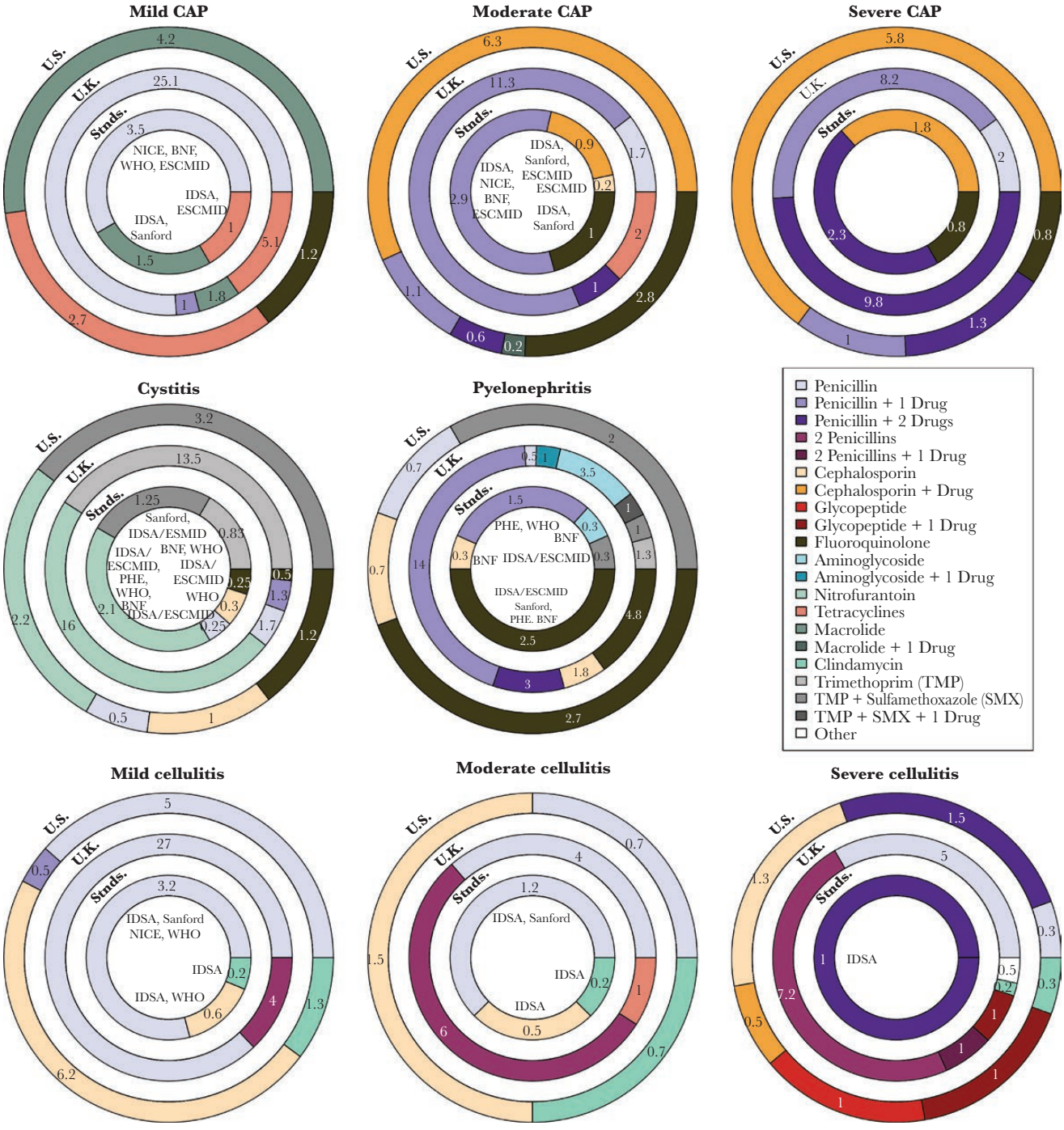

Figure 2. Discordance among guidance documents and regional standards for common infections. For each type of infection, antibiotic recommendations are presented for US hospitals (outer ring), UK hospitals (middle ring), and regional standards (Stnds.; inner ring). The key is organized according to antibiotic class, and color saturation increases as the number of drugs in the recommendation increases. The number within the ring subsections corresponds to the total normalized recommendations made for an antibiotic class, such that the sum of recommendations equals the number of hospitals included in each ring. Agreement between antibiotics recommended by hospitals in the United States or United Kingdom with regional standards is reflected by a sharing of the same colors within rings. For example, agreement decreases between US or UK hospital guidance and regional standards as one moves from mild to moderate to severe cellulitis, as reflected by diminished light blue (ie, penicillin) bars shared by the respective rings. Overall, hospital guidance documents differed considerably in prescription recommendations, as did regional standards. US and UK hospitals generally made differing recommendations, with the United Kingdom recommending penicillins for baseline treatment, while the United States recommended cephalosporins. The United States also recommended fluoroquinolones, while the United Kingdom did rarely, except for in the case of pyelonephritis. The variety of recommendations generally increased with severity of infection (ie, from left to right).

susceptibilities did not clearly align with observed recommendation patterns.

Similarly, we used hospital-reported cost data to investigate cost as an explanation for regional prescribing patterns. Costs according to method of administration were collected from our corpus for oral (PO) and intravenous (IV) treatment of CAP (n = 6 and 4, respectively), UTI PO (n = 4) and IV (n = 4), and cellulitis PO (n = 5) and IV (n = 5). Hospitals recommended the cheapest drug 32.5% of the time (Supplementary Figure 5). All observed frequencies fell within a 95% confidence interval for expectations due to chance (Supplementary Table 5). Thus, cost was also insufficient to explain recommendation differences, although we note that this could be due to the small number of guidelines that included cost information.

In evaluating studies cited by regional standards, we found few studies in support of each recommendation (Supplementary Figure 6). Regional standards cited the same study in only 3 instances. However, the studies were used to support different recommendations, which was reasonable considering the studies' noninferiority findings and the fact that guideline committees are not tasked with comprehensively citing the existing literature base. Moreover, an investigation of 10% (n = 130) of randomly selected PubMed hits for CAP diagnosis and recommendations revealed that few (29.2%, n = 38) publications compared multiple antibiotics for effectiveness, and of those, most (73.7%, n = 28) were noninferiority studies. Taken together, our results suggest that an ambiguous evidence base for superior recommendations is the major driver behind variability in regional standards, and this variability is amplified by hospitals' choice of recommendations for their own guidelines.

DISCUSSION

In this study, we investigated the global landscape of publicly available antibiotic prescription guidelines published in English, finding substantial variability in structure, content, and recommendations. There were clear regional recommendation patterns in the United States and United Kingdom. In the United States, cephalosporins were generally preferred over penicillins, whereas the reverse pattern was observed in the United Kingdom. The United States also preferentially recommended fluoroquinolones, while these agents were rarely recommended in the United Kingdom. The differences in recommendations are likely due to regional regulation of fluoroquinolones, which are associated with uncommon but disabling and potentially long-lasting side effects. Based on these uncommon reports, the US Food and Drug Administration in 2016 warned that the risk of serious side effects of fluoroquinolones generally outweighed benefits for patients with uncomplicated infections in whom other treatment alternatives were available. The UK Medicines & Healthcare products Regulatory Agency statement was firmer. In 2019, it published new restrictions and precautions for fluoroquinolones, which are authorized only for use in serious, life-threatening bacterial infections [32]. Additionally, prescribing patterns could not be attributed to differences in regional antibiotic resistance or cost. Rather, the lack of consensus seemed to emanate from a dearth of studies designed to determine superior treatment options, leaving the possibility for standards to vary when interpreting the same literature base. With this conclusion, we nevertheless recognize that the antibiotic prescription recommendations endorsed by clinical institutions are a result of a multifaceted, complex decision. Additionally, we recognize that hospital guidance documents' adherence to regional standards is not mandatory. Therefore, even with a clear evidence base, some degree of variability among guidelines would be expected.

Upon first consideration, our findings might be interpreted as suggesting that guideline consistency and clarity would be improved if clinical trials pursued superiority rather than noninferiority end points. However, antibiotics for infections such as CAP are often very effective when caused by susceptible organisms. Thus, demonstration of superiority of a new drug is unlikely [33–35], and achieving sufficient sample sizes for such trials is typically prohibitive [36]. For these reasons, noninferiority designs are necessary and the only reasonable and scientifically valid approach to facilitate US Food and Drug Administration and European Medicines Agency approval of new antibiotics [35]. Novel study designs and outcome assessments for evaluating antimicrobial efficacy may assist in guideline formulation. Desirability of Outcome Ranking (DOOR) and Response Adjusted for Duration of Antibiotic Risk (RADAR) designs use a 2-step process to compare strategies of antibiotic optimization by considering hierarchies of efficacy and possible harm to patients [37]. DOOR and RADAR potentially reduce sample sizes compared with traditional superiority and even noninferiority trials, making studies more feasible [38]. At a recent workshop for enhancing drug development, the NIH Antimicrobial Resistance Leadership Group advocated for funding of studies that answer specific clinical questions about optimal treatment for common infections [39, 40]. Proposals for alternative antibiotic study designs have yet to be broadly implemented, and guidelines based on systematic reviews of clinical trial data are unlikely to arrive at unambiguous recommendations. The IDSA is exploring novel models for developing and rapidly disseminating treatment recommendations that are less stringently tied to formal Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria [41].

Other suggestions for improving guidelines stem from our data. Due to the observed wide variability in structure, content, and recommendations—corroborated by other guideline recommendation variation studies [14–16]—we suggest that policy-makers provide best practices for hospital guidance document construction to achieve greater standardization and

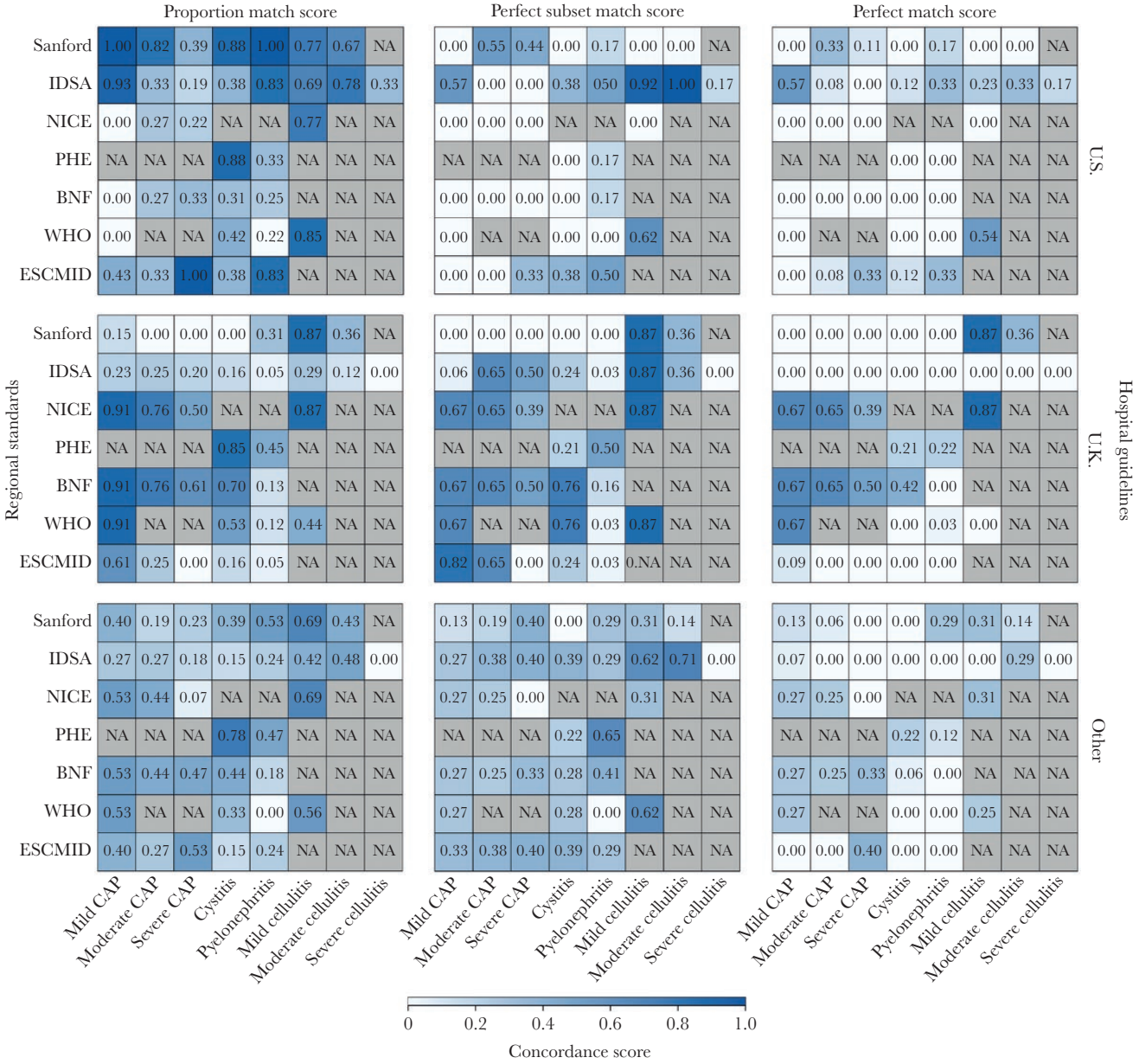

Figure 3. Modest concordance of hospital guidance documents to regional standards. Average concordance scores within the 3 geographical groupings were mapped to each of the 7 regional standards at the level of antibiotic class. Concordance of recommendations based on their antibiotic class was lower for the US and Other guidelines than UK guidelines with their respective regional standards. Gray represents a mapping that is not applicable due to the regional standard not making a recommendation for that clinical indication.

ease the burden of document maintenance. In addition, as concordance was greater for classes of antibiotics (Figure 3) than for particular drugs (Supplementary Figure 2), regional standards could consider providing class-level recommendations, as demonstrated in the 2019 IDSA CAP update [42]. Class-level recommendations require less specific evidence in support of a single antibiotic and remain forward compatible as next-generation antibiotics are added to a class. Furthermore, class-level recommendations provide leeway for hospital guidance documents to make within-class decisions according to antibiotic availability, local susceptibility, and clinician preference. In considering forward compatibility for hospitals, we suggest that guidance documents are revisited at least annually.

Our study has a number of limitations. We only included guidelines written in English that were publicly available, which may have resulted in an over-representation of UK guidelines due to their National Health System. There were many countries for which we did not locate guidance documents, and we encourage more hospitals to make their documents open source and readily available to the public. Similarly, our search might

have omitted documents based on our queries and search engines, although effort was taken to include as many guidance documents as possible. Also, cost information was based on a few hospital representatives for each region because most guidance documents did not include cost data. Additionally, US hospitals will likely update recommendations in accordance with the 2019 IDSA CAP guideline, which no longer provides separate recommendations for moderate and severe CAP, but rather places a priority on identifying local risk factors for multidrug-resistant pathogens. Another development from the 2019 IDSA update is the addition of penicillin as an appropriate outpatient treatment, which was not previously noted and does not follow the recommendation pattern we observed in the United States. However, this finding emphasizes that penicillins are a viable empiric therapy for CAP [42].

We hope that this study adds an objective perspective to the ongoing dialogue about high variability in antibiotic prescribing. Variation in antibiotic prescribing is multipronged: Clinicians exhibit low adherence to hospital guidance documents, hospitals exhibit variable adherence to standards, and rarely is evidence provided that would explain parting from regional standard recommendations. We are optimistic that novel study designs might provide more clinically relevant data in the future, and new models for treatment guidance can be developed that combine evidence from high-quality research with unambiguous recommendations for clinicians.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Patient consent. No patients partook in this work.

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