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Assessment of empirical antibiotic therapy optimisation in six hospitals: an observational cohort study

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See **Online** for appendix

Contributors

NPB and DJM had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. RL, DJM, EP, MLS, ES, AS, and SAW were responsible for the conception and design of the study. JC, TK, DJM, BJ, DZU, SAW, and HY were responsible for the acquisition of the data. NPB, RL, DJM, EP, MLS, ES, and AS did the analysis and interpretation of the data. NPB and DJM drafted the manuscript. All authors were responsible for critical revision of the manuscript for important intellectual content. NPB, DJM, and MLS did the statistical analysis. RL, DJM, EP, ES, and AS obtained funding. ES and MLS gave administrative, technical, or material support. NPB, RL, and AS supervised the study.

Declaration of interests

DJM is a research consultant for Sanogiene and Welch Allyn (not related to this work). ES is a member of a 3-M medical advisory board and Sage's speaker's bureau (not related to this work). All other authors have no competing interests.

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Summary

Background—Modification of empirical antimicrobials when warranted by culture results or clinical signs is recommended to control antimicrobial overuse and resistance. We aimed to assess the frequency with which patients were started on empirical antimicrobials, characteristics of the empirical regimen and the clinical characteristics of patients at the time of starting antimicrobials, patterns of changes to empirical therapy at different timepoints, and modifiable factors associated with changes to the initial empirical regimen in the first 5 days of therapy.

Methods—We did a chart review of adult inpatients receiving one or more antimicrobials in six US hospitals on 4 days during 2009 and 2010. Our primary outcome was the modification of antimicrobial regimen on or before the 5th day of empirical therapy, analysed as a three-category variable. Bivariate analyses were used to establish demographic and clinical variables associated with the outcome. Variables with p values below 0.1 were included in a multivariable generalised linear latent and mixed model with multinomial logit link to adjust for clustering within hospitals and accommodate a non-binary outcome variable.

Findings—Across the six study sites, 4119 (60%) of 6812 inpatients received antimicrobials. Of 1200 randomly selected patients with active antimicrobials, 730 (61%) met inclusion criteria. At the start of therapy, 220 (30%) patients were afebrile and had normal white blood cell counts. Appropriate cultures were collected from 432 (59%) patients, and 250 (58%) were negative. By the 5th day of therapy, 12·5% of empirical antimicrobials were escalated, 21·5% were narrowed or discontinued, and 66·4% were unchanged. Narrowing or discontinuation was more likely when cultures were collected at the start of therapy (adjusted OR 1·68, 95% CI 1·05–2·70) and no infection was noted on an initial radiological study (1·76, 1·11–2·79). Escalation was associated with multiple infection sites (2·54, 1·34–4·83) and a positive culture (1·99, 1·20–3·29).

Interpretation—Broad-spectrum empirical therapy is common, even when clinical signs of infection are absent. Fewer than one in three inpatients have their regimens narrowed within 5 days of starting empirical antimicrobials. Improved diagnostic methods and continued education are needed to guide discontinuation of antimicrobials.

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Introduction

Infections with multidrug-resistant bacteria are associated with substantial mortality and morbidity[1] and are becoming more common in hospitals worldwide. Overprescribing of antimicrobials is a major factor driving the development of resistance.[2] Broad-spectrum antimicrobial use in hospitals is often excessive and unnecessarily prolonged,[3,4] which has led to calls for wider and more effective implementation of antimicrobial stewardship in the inpatient setting.[3,5]

Antimicrobial stewardship programmes aim to minimise unnecessary or inappropriate therapy, typically through restriction or audit and review of antimicrobial orders. One common strategy, therapy optimisation, initiates empirical coverage with minimal delay, followed by discontinuation or streamlining to a regimen with the narrowest possible spectrum based on relevant diagnostic information.[6] The initial reassessment should occur as early as culture data are available, at which point clinical improvement and bacteriological results usually allow the removal of one or more antimicrobials.[6,7]

To our knowledge, there are no patient-level, multicentre studies describing how often and in what clinical context optimisation of empirical antimicrobial use occurs in the general hospital population. Characterising patterns and factors associated with the start, stop, and change of modifiable empirical therapy is the key to identifying opportunities to reduce unnecessary antimicrobial exposure, which can minimise the development of resistance and adverse events.[8,9]

In a cohort of inpatients receiving antimicrobials and hospitalised in six acute-care hospitals, we aimed to assess the frequency with which patients were started on empirical antimicrobials, characteristics of the empirical regimen and the clinical characteristics of patients at the time of starting antimicrobials, patterns of changes to empirical therapy at different timepoints, and modifiable factors associated with changes to the initial empirical regimen in the first 5 days of therapy, such as the availability of microbiological and imaging information.

Methods

Setting

A convenience sample of six facilities of diverse size, type, and geographical location were recruited for the study, including two university-affiliated teaching hospitals in the midwest and Pacific regions, a public community hospital in the mid-Atlantic, and three private

community hospitals in the south, mountain, and Pacific regions of the USA with bed sizes ranging from 125 to 700.

We asked collaborators who worked in a range of hospitals (types and geographical regions) for their involvement. When designing the study, we recruited a diverse team of infectious disease specialists (most of whom were members of the Emerging Infections Network) and asked for their facility's ability to provide data and willingness to participate. Because most of these contacts were affiliated with large teaching centres, we also contacted private hospital networks so that private community hospitals were represented. Some of these hospitals did not have infectious disease specialists on site that could review the charts. To avoid excluding sites where this was the case, we hired infectious disease physicians from outside facilities to review charts. Facility characteristics are summarised in the appendix.

At the time of the study, two sites had full electronic records, three had electronic systems with scanned handwritten notes, and one had a full paper-based system. None used rapid diagnostic microbiology techniques. Three of the six sites had antimicrobial stewardship programmes: two centres needed pre-authorisation by an on-call infectious disease specialist that could be obtained over the phone before restricted agents are dispensed, and distributed booklets with facility antibiograms and antimicrobial guidelines, including prescribing criteria and cost of therapy days. The other site with an antimicrobial stewardship programme did not restrict antimicrobials, but had a clinical pharmacist who did daily prospective audits with feedback to prescribers, consisting of an informal consultation with non-binding suggestions on optimising the choice and administration of therapy, in addition to formal protocols on intravenous to oral conversion, pharmacodynamic dosing, and renal adjustment of doses. All sites had pharmacy and therapeutics com mittees and restricted formularies with facility-specific criteria for dispensing certain antimicrobials. None had antimicrobial timeout protocols that restricted the duration of empirical antimicrobial prescriptions, or educational interventions specifically focused on streamlining antimicrobial prescribing.

Study design

Patient charts were randomly identified from the daily inpatient census for four review dates chosen at equal intervals through the study period (Nov 20, 2009; Feb 10, 2010; May 20, 2010; Aug 10, 2010). Research coordinators at each site merged lists of hospitalised patients with pharmacy databases to filter out patients not receiving antimicrobials on these dates, sorted the resulting list at random, and provided data collectors access to the corresponding medical records. Randomisation was done with Microsoft Excel (version 14.2): a variable of random numbers were generated using the RAND() function without replacement. Rows or patient identifiers were then sorted by the numbers in that column. This was done by the study coordinators at each site.

200 records (50 per review date) matching our inclusion criteria were enrolled at each site: non-paediatric admission (older than 18 years), hospitalised for more than 24 h in non-psychiatric wards, and active order for antimicrobial prescription on the review date. If there were fewer than 50 eligible cases for any of the index dates, reviewers added inpatient charts from a date 2 weeks beyond the index date.

Infectious disease specialists reviewed charts at each site, recording patient demographics, outpatient antimicrobial use and allergies, and the name, indication, start and stop dates, and documentation source, with a standardised electronic form.[10] When documentation for starting or stopping antimicrobials was conflicting, reviewers were asked to make a clinical judgment based on all the information available in the record. A training session was held with a sample of ten de-identified charts randomly chosen from participating facilities to pilot the tool and assess inter-rater reliability. Agreement coefficients (κ) were within satisfactory range for all fields (0·8–1).

International Classification of Diseases, ninth revision (ICD-9) codes were extracted and used to calculate the Charlson comorbidity score.[11] The isolate source, hospital day of specimen collection, and culture result were recorded for all cultures collected within 72 h before and up to 14 days after the start of the earliest recorded antimicrobial. Other diagnostic information recorded included a single reading of body temperature closest to and within 12 h of starting antibiotics, a single reading of white blood cell (WBC) count closest to and within 24 h, and all radiological studies within 72 h of starting any antimicrobial prescription. Microbiology and radiology studies were deemed relevant to this analysis if they were collected on or before the day antibiotic therapy was started. Patients were deemed immunocompromised if they had HIV with a CD4 cell count less than 200 cells per μL, neutropenia, bone marrow or solid organ transplant, or late-stage cancer. The Sabadell modification of the McCabe-Jackson score was used to assign prognosis at discharge and included four subjective categories: good prognosis, poor long-term prognosis (>6 months) with unlimited intensive care unit (ICU) readmission, poor short-term prognosis (<6 months) with debatable ICU readmission, and death expected during hospitalisation with ICU readmission not recommended.[12]

Review of therapy adjustments

The analysis was further focused on patterns and factors associated with the decision to modify antimicrobial therapy in the first 5 days of treatment. We excluded all patients who received antimicrobials exclusively for a prophylactic indication, were discharged in less than 3 days after the start of the earliest recorded antimicrobial, and received pathogen-directed therapy from the start of treatment.

All remaining antimicrobial courses were judged to have been started empirically and were classified as narrowed or discontinued, escalated, or unchanged, based on criteria used by Kollef and colleagues.[13] We defined narrowed or discontinued regimens as a change in the spectrum or number of prescribed antimicrobials that resulted in a narrower spectrum of coverage, or the ordered early cessation of inpatient antimicrobial therapy. The latter category included patients who were discharged and sent home with a pre scription for outpatient antimicrobials. Escalation was defined as an increase in spectrum or number of anti microbials or both. Cases were classified as unchanged when the regimen was continued without adjustments for the indicated duration, or switched to an equivalent spectrum.

Change in antimicrobial spectrum was assessed by applying several modified criteria to rank antimicrobials in ascending order by their relative activity against drug-resistant organisms: narrow spectrum (rank 1), including first-generation and second-generation cephalosporins,

amoxicillin, co-trimoxazole, nafcillin, and metronidazole; broad spectrum (rank 2), including fluoroquinolones, macrolides, third-generation cephalosporins, co-amoxiclav, clindamycin, and oral vancomycin; extended spectrum (rank 3), including antipseudomonal penicillins, cefepime, ertapenem, and intravenous vancomycin; and restricted (rank 4), including antipseudomonal carbapenems, colistin, tigecycline, linezolid, and daptomycin. Therapy adjustments that occurred exclusively because of antimicrobial-related adverse events were classified as unchanged since this was not seen as evidence of reassessing appropriateness of therapy for infection (adverse events only lead to the reassessment of a small fraction of cases [n=13] where patients were switched to second-line agents due to allergies or other intolerable side-effects, but the resulting spectrum of the replacement was not equivalent to that of the initial regimen). Changes from intravenous to per oral route were not assessed because the route of administration was not recorded (except in the case of vancomycin).

The site of infection was based on the prescribing indication for the initial course, as documented in physician notes, order sets, and the discharge summary. Culture results were deemed relevant to therapy change if an organism not part of normal flora was isolated from the suspected site of infection during the course of treatment. Radiology results were deemed relevant if the radiology image report showed infection.

Statistical analysis

Our primary outcome was the modification of the antimicrobial regimen on or before the 5th day of empirical therapy, analysed as a three-category variable with unchanged by that day as the reference group. The 5th day was chosen because by this time clinical information relevant to therapy optimisation, such as culture and sensitivity results, would be available.

Bivariate analyses were used to establish demographic and clinical variables associated with the outcome. The narrowed or discontinued and escalated groups were individually compared with the unchanged group. Differences between groups were assessed with χ^2 or Fisher's exact test for categorical variables, and Student t-test or Wilcoxon rank-sum test for continuous variables. Variables with p values below 0·1 were included in a multivariable generalised linear latent and mixed model with multinomial logit link to adjust for clustering within hospitals and accommodate a non-binary outcome variable.[14] Modifiable factors, such as the collection of microbiological cultures and radiology before or on the same day as the start of therapy, were forced in all models. Other variables with p values below 0·1 in bivariate analyses were added in order of the size of their unadjusted odds ratios, and were left in the model based on results of a likelihood ratio test. Statistical significance was defined as a p value below 0·05. All analysis was done in Stata version 11 (Stata Corp).

Role of the funding source

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Results

Across the six hospitals, 6812 patients were admitted to hospital on the four review dates, of whom 4119 (60%) had an active antimicrobial order ranging from 46·6% in a community hospital to 78·8% in a teaching facility (appendix). Of these, reviewers enrolled 1200 randomly selected non-duplicate charts of non-psychiatric, non-paediatric admissions. Patients who received exclusively prophylactic courses (n=282), had a length of stay shorter than 3 days after the start of the earliest empirical antimicrobial (n=90), or had an identified pathogen from the start of therapy (n=98) were excluded (figure 1).

For the remaining 730 patients, broad-spectrum and extended-spectrum antimicrobial regimens accounted for the most empirical use (figure 2). Fluoroquinolone monotherapy, classified under rank 2, was the most common prescription (18%). Piperacillin–tazobactam and vancomycin, alone and in combination, accounted for more than 22% of regimens, followed by third-generation cephalosporins (3·8%). The appendix lists the most common regimens by site of infection.

For the 730 patients in the analysis, table 1 shows the available diagnostic information at time of starting antimicrobials by site of infection. At start of therapy, normal WBC count (defined as >4000 or <12 000 cells per μL) was present in 277 (38%) patients. 491 (67%) patients did not have fever, and 220 (30%) had neither a high WBC count nor fever. Patients with infections of the urinary tract (39 [37%]) and respiratory system (94 [35%]) probably had neither fever nor abnormal WBC count.

Overall, microbiological cultures were collected on or before day 1 of therapy in 432 (59%) patients, and 250 (58%) of those were negative. Of patients with presumed urinary or bloodstream infections, where culture yields tend to be higher, 27 (26%) and 22 (27%), respectively, had negative cultures from the suspected infection site. 22 (37%) of 59 patients with negative urine culture and 11 (50%) of 22 of those with negative blood culture had antimicrobials stopped or narrowed. 101 (14%) of 730 patients had cultures obtained after start of antibiotics and before day 5, and only 29 (29%) of those were positive.

450 (62%) patients had an imaging study on or before day 1 of therapy. Results did not suggest infection for 229 (31%) patients, or roughly half of those with available results. Of patients with presumed respiratory infections, a chest imaging study was done for 186 (68%), and less than a third of those had negative results. 12 (24%) of 50 of those patients with negative chest imaging had their antimicrobials narrowed or discontinued. 78 (11%) of 730 patients had imaging after start of antibiotics and before day 5, and 44 (56%) of those noted an infection.

Narrowing or discontinuation occurred in 211 (29%) of 730 patients at any point after a course was started, 69 (9%) by day 3 and 157 (22%) by day 5 (figure 1). Across facilities,

this proportion ranged between seven (8%) at a large teaching facility and 37 (30%) at a community hospital, both of which lacked stewardship programmes (appendix). The median duration before courses were narrowed, discontinued, or escalated was 4·0 days (IQR 3·0–5·0) and 4·5 days (IQR 3·0–6·0), respectively. Both were different from the median total duration of unchanged courses (5·5 days, 3·0–8·0; $p<0·001$ by Wilcoxon rank-sum test). The time between the start of therapy and change varied across infection sites, but the most adjustments occurred before or on the 5th day, which was used as the cutoff time in our analysis (appendix).

Hospital teaching status, patient age, Charlson comorbidity score, modified McCabe-Jackson score, reported allergies, abnormal WBC count, and being immunocompromised were not associated with either escalation, narrowing, or discontinuation by day 5 (appendix).

Comparing unchanged with narrowed or discontinued cases in the first 5 days of therapy, patients with pretherapy length of stay longer than a day ($p=0·01$) and those started on extended-spectrum antimicrobials (rank 3 of 4, mainly vancomycin and piperacillin–tazobactam) were more likely to have their therapy narrowed or discontinued ($p<0·001$; table 2). Across infection sites, narrowing or discontinuation was more common for urinary tract infections ($p=0·02$) and when more than one site was suspected as the origin of infection ($p=0·05$). Narrowing or discontinuation was more likely to occur when a culture ($p=0·001$) or imaging study ($p=0·01$) were ordered at the start of therapy, and when the imaging study showed no signs of infection ($p=0·001$). A positive culture result at any point of therapy was also associated with a narrowed or discontinued outcome ($p=0·05$). Admission to a non-teaching facility ($p=0·1$) or one with preauthorisation or prospective review antimicrobial stewardship programme ($p=0·07$) seemed to show an association with narrowing or deescalation and were included in the selection procedure for the multivariable model; however, the lack of significance makes the strength of this association unclear.

When comparing escalations with unchanged cases in the first 5 days (table 3), escalated cases were more likely to be admitted to the ICU ($p=0·03$), have multiple infection sites ($p<0·001$), a fever at start of therapy ($p=0·05$), yield a positive culture at the start of therapy ($p=0·003$), and have a positive culture ($p=0·05$) or imaging suggestive of infection ($p=0·04$) obtained between the 1st and 5th days of therapy. Escalated cases were also more likely to be started on monotherapy ($p=0·02$), and their spectrum of the regimen seemed to be narrower ($p=0·06$); however, this association is uncertain in view of the lack of significance. The ordering of imaging or culture studies were not associated with escalation by day 5.

Table 4 shows results for the final generalised linear latent and mixed model for change to therapy by day 5, modelled as a three-level variable, with unchanged as the reference group. Controlling for the spectrum of activity of the initial regimen, the collection of microbiological culture at the start of therapy was associated with narrowing or discontinuation of therapy (adjusted odds ratio [OR] 1·68, 95% CI 1·05–2·70), as was the lack of infection noted on an imaging study (OR 1·76, 1·11–2·79). Escalation was associated with multiple infection sites (OR 2·54, 1·34–4·83) and the presence of a positive culture (OR

1·99, 1·2–3·29). The ordering of imaging studies was not associated with either outcome, and neither were facility-level factors.

Discussion

In the largest study, to our knowledge, of the frequency and determinants of changes to empirical antimicrobial therapy we found that antimicrobial use was highly prevalent, with nearly 60% of inpatients receiving antimicrobials; laboratory and imaging studies often did not suggest infection; most initial regimens included broad-spectrum and extended-spectrum drugs; cultures and imaging studies were often not obtained at the start of therapy, even for suspected urinary, respiratory, and bloodstream infections, and when results were negative, fewer than half of patients had their antimicrobials stopped or narrowed; and after controlling for clinical factors, obtaining a culture and imaging study at the start of therapy were associated with narrowing or earlier cessation of antibiotics (panel).

In our study, at the time of starting antimicrobials, about a third of patients did not have a fever or abnormal WBC count, and half of the ordered radiology and microbiology results did not identify an infection. These results suggest a large proportion of antimicrobial use could have been avoided. This finding is consistent with other studies reporting that up to half of antimicrobials started in hospitals are unnecessary,[26,27] and that 37% of common prescribing scenarios (for urinary tract infections and intravenous vancomycin) could be improved through better use of diagnostic testing.[3]

Strategies to optimise empirical therapy focus on collecting relevant imaging and cultures at time of starting antimicrobials.[28] Although we identified evidence suggesting that both practices lead to less antibiotic use, the collection of cultures at time of starting antimicrobials had a stronger effect on later change in therapy. This finding agrees with previous reports that optimal antibiotic use is highly dependent on identification of a causative organism.[29,30] As a result of the rising prevalence of antibiotic-resistant infections, appropriate specimen collection before starting antibiotics is a crucial part of diagnostic workup for patients with infections who need a hospital stay. Additional strategies of rapid pathogen identification by mass spectrometry and nucleic acid testing,[31] or other markers of infection such as procalcitonin are being assessed and might provide additional benefit in appropriate antibiotic usage.[32] Rapid diagnostic tests were not used at any of the facilities at the time of our study and could not be assessed.

The appropriate frequency of narrowing or escalating therapy is unknown and depends on the indication for antimicrobials and severity of illness of the patient. In our study, the teaching hospital with a large surgical centre had the lowest frequency of narrowing therapy and highest antibiotic usage and longest length of stay, probably because of the high complexity of cases. Although it is beyond the scope of our study to determine whether this use rate was optimal, prospective studies focusing on specific infections and controlling for these factors have noted frequently missed streamlining opportunities in hospital-associated pneumonia,[7] *Staphylococcus aureus* bloodstream infection,[33] and complicated urinary tract infections.[19]

Our study has limitations. Although based on previous research,[13] our ranking of antibiotic activity not been broadly applied in the inpatient context and classification of antibiotics has a subjective element—eg, extended-spectrum vancomycin versus restricted daptomycin. This subjectivity restricts our ability to compare results with earlier studies. Although we included six diverse hospitals (representing the three main types of hospital), this is a convenience sample, restricting our ability to generalise and our power to analyse facility-level factors, including teaching status or presence of an antimicrobial stewardship programme. We collected data on comorbidities and prognosis at discharge but were unable to control for severity of illness because of the retrospective design of our study. As a result of this limitation and because we did not consider the susceptibilities of clinical cultures, we could not assess the appropriateness of empirical therapy and whether more optimal treatment alternatives existed. We did not collect data on steroid use at time of antibiotic start, which might mask the presence of infection measured by fever, and generally, patients with active infections might not always present with fever or abnormal WBC count. Dose and route of administration were not considered, although pharmacy-driven interventions such as pharmacodynamic dosing protocols can be an important supplemental antimicrobial stewardship programme strategy. Finally, although we trained infectious disease physicians to collect data, an inherent limitation of all multicentre chart review studies is variability in the quality of documentation across sites and cases.

Despite these limitations, this work has important implications as the first US-based multisite investigation to describe patterns of re-assessing inpatient antimicrobial use. We emphasise several targets for improving the prescribing of antimicrobials. Prescribers and other stakeholders should encourage timely acquisition of microbiological samples. We noted that obtaining cultures was a predictor of narrowing or stopping therapy, but cultures were not universally obtained when indicated. Physicians should focus on patients started on antimicrobials in the absence of common infection indicators, such as fever and abnormal WBC counts. One would expect some instances where these might not be present, but the finding that they were absent in about a third of the patients in this study was unexpected and suggests an opportunity for improvement. Suspected respiratory, bloodstream, and urinary tract infections—conditions where negative imaging or culture results strongly suggest the absence of an infection—present major opportunities to avoid unnecessary antimicrobials. Finally, to improve hospital-wide antimicrobial use, antimicrobial stewardship programmes must develop universal criteria and oversight mechanisms for optimal prescribing that address all patients on empirical therapy, since both broad-spectrum and narrow-spectrum antimicrobials are often used inappropriately in response to clinical uncertainty. Such a culture change will need all providers to be better trained in the appropriate use of antimicrobials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Panel: Research in context

Systematic review

We searched PubMed and Google Scholar for reports published in English before June 25, 2014, with the terms “de-escalation”, “antibiotic stewardship”, “streamlining”, and “point prevalence of inpatient antimicrobial use”. The largest and most recent benchmarking study of inpatient antibiotic use reports 56% of patients discharged from 323 US hospitals had received an antibiotic.[3] Another analysis of 70 US teaching hospitals showed 64% of inpatients received antimicrobial therapy,[15] and a growing majority of that use was broad-spectrum antimicrobials.[16] Similar studies of French[17] and Dutch[18] hospitals showed that 41% and 30% of patients were on antimicrobials, respectively. Strategies to optimise prescribing, also termed “antimicrobial timeout” or “de-escalation”, have been studied in distinct populations defined by diagnosis,[19,20] use of a specific antimicrobial,[21,22] or intensive care unit status.[23,24] De-escalation of empirical therapy has been associated with improved survival among critical-care patients with health-care-associated pneumonia and sepsis.[13,25]

Interpretation

The finding that nearly two-thirds of patients receive antimicrobials is consistent with studies from North America, and higher than the rate reported by European studies. Also consistent with the literature, there was wide variability in the prevalence of therapy across sites: one teaching institution reported 78% of patients had an active antimicrobial order. However, a large share of that was surgical prophylaxis, resulting in fewer included cases from that site. Although de-escalation is recommended by the Centers for Disease Control and Prevention for all hospitalised patients,[3,5] its frequency has not been studied across a general hospital population. This study provides the first assessment of de-escalation in hospitalised patients. The low rate of de-escalation indicates substantial room for improvement in antimicrobial management.

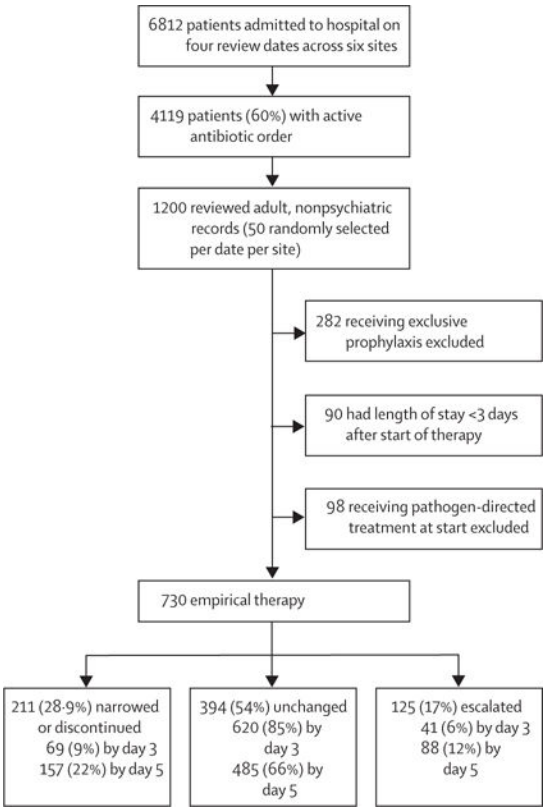

Figure 1.
Study profile

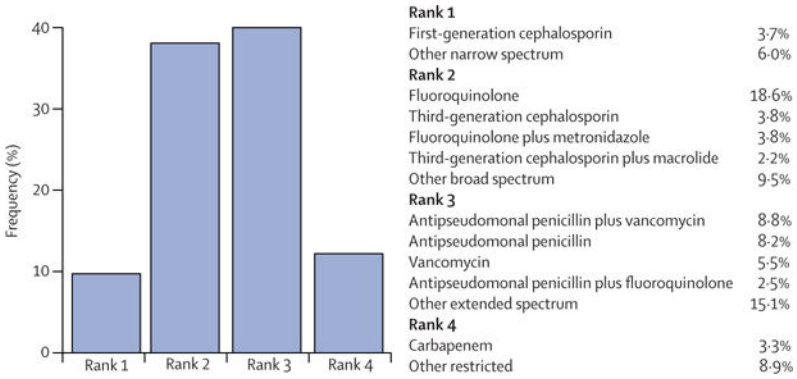

Figure 2. Initial empirical regimens ranked by spectrum of activity (n=730 patients)

Ranking corresponds to the spectrum of activity: from 1 (lowest) to 4 (highest). The relative frequency of the ten most common regimens is shown separately. See appendix for a breakdown of regimens by infection site. Narrow-spectrum (rank 1), including courses where the drug with the broadest spectrum was any of the following: first-generation or second-generation cephalosporins, amoxicillin, co-trimoxazole, nafcillin, and metronidazole. Broad spectrum (rank 2), including courses where the drug with the broadest spectrum was any of the following: fluoroquinolones, extended-spectrum macrolides, third-generation cephalosporins, co-amoxiclav, clindamycin, and oral vancomycin. Extended spectrum (rank 3), including courses where the drug with the broadest spectrum was any of the following: antipseudomonal penicillins, cefepime, ertapenem, and intravenous vancomycin. Restricted (rank 4), including courses where the drug with the broadest spectrum was any of the following: antipseudomonal carbapenems, colistin, tigecycline, linezolid, and daptomycin.

Table 1

Relative frequency of diagnostic information for patients started on an empirical antimicrobial regimen, by site of infection

	Total (n=730)	Respiratory (n=272)	Urinary tract (n=105)	Soft tissue (n=115)	Gastrointestinal (n=91)	Bloodstream (n=82)	Other (n=65)
WBC count							
Normal	277 (38%)	123 (45%)	45 (43%)	43 (37%)	20 (22%)	31 (38%)	15 (23%)
Abnormal	233 (32%)	78 (29%)	28 (27%)	36 (31%)	33 (36%)	33 (40%)	25 (39%)
No data	220 (30%)	71 (26%)	32 (31%)	36 (31%)	38 (42%)	18 (22%)	25 (39%)
Body temperature							
Normal	491 (67%)	185 (68%)	70 (67%)	93 (81%)	63 (69%)	39 (48%)	41 (63%)
Abnormal	239 (33%)	87 (32%)	35 (33%)	22 (19%)	28 (31%)	43 (52%)	24 (37%)
Body temperature and WBC							
Normal	220 (30%)	94 (35%)	39 (37%)	39 (34%)	17 (19%)	17 (21%)	14 (22%)
Abnormal	290 (40%)	107 (39%)	34 (32%)	40 (35%)	36 (40%)	47 (57%)	26 (40%)
No data	220 (30%)	71 (26%)	32 (31%)	36 (31%)	38 (42%)	18 (22%)	25 (39%)
Imaging study at start of antimicrobials							
Yes	450 (62%)	186 (68%)	69 (66%)	56 (49%)	57 (63%)	46 (56%)	36 (55%)
No	280 (38%)	86 (32%)	36 (34%)	59 (51%)	34 (37%)	36 (44%)	29 (45%)
Sign of infection on imaging study done at start of antimicrobials							
Yes	221 (30%)	136 (50%)	10 (10%)	16 (14%)	30 (33%)	14 (17%)	15 (23%)
No	229 (31%)	50 (18%)	59 (56%)	40 (35%)	27 (30%)	32 (39%)	21 (32%)
No study	280 (38%)	86 (32%)	36 (34%)	59 (51%)	34 (37%)	36 (44%)	29 (45%)
Culture collected at start of antimicrobials							
Yes	432 (59%)	181 (67%)	77 (73%)	59 (51%)	34 (37%)	45 (55%)	36 (55%)
No	298 (41%)	91 (34%)	28 (27%)	56 (49%)	57 (63%)	37 (45%)	29 (45%)
Culture collected at start of antimicrobials							
Negative	250 (34%)	129 (47%)	27 (26%)	30 (26%)	26 (29%)	22 (27%)	23 (35%)
Positive	182 (25%)	52 (19%)	50 (48%)	29 (25%)	8 (9%)	23 (28%)	13 (20%)
No culture	298 (41%)	91 (34%)	28 (27%)	56 (49%)	57 (63%)	37 (45%)	29 (45%)

Data are n (%). Numbers might not add to 100% because of rounding. Normal white blood cell (WBC) defined as leucocyte count more than 4000 or less than 12 000 cells per μL. Normal body temperature defined as between 35°C and 38°C. Imaging or culture performed defined as any radiological or bacteriological study done on the same day or before start of antimicrobial therapy.

Table 2

Factors associated with modifying initial empirical regimens on or before 5th day of therapy and considered for inclusion in the model (p<0·1): narrow or discontinued versus unchanged

	Narrowed or discontinued (n=157)	Unchanged (n=485)	p value
Pre-therapy LOS >1 day	40 (25%)	177 (36%)	0·01
Stewardship programme			
No programme	62 (39%)	241 (50%)	0·07
Pre-authorisation	65 (41%)	160 (33%)	
Prospective review	30 (19%)	84 (17%)	
Relative activity of initial regimen against drug-resistant organisms (rank 1–4)*			<0·001
Narrow spectrum (rank 1)	8 (5%)	50 (10%)	
Broad spectrum (rank 2)	43 (27%)	191 (39%)	
Extended spectrum (rank 3)	92 (59%)	179 (37%)	
Restricted (rank 4)	14 (9%)	65 (13%)	
Urinary tract infection	31 (20%)	59 (12%)	0·02
Multiple infection sites	21 (13%)	39 (8%)	0·05
Imaging study done at start of antimicrobials	110 (70%)	286 (59%)	0·01
No sign of infection on imaging study done at start of antimicrobials	66 (42%)	135 (28%)	0·001
Culture collected at start of antimicrobials	111 (71%)	271 (56%)	0·001
Positive culture from specimen collected at start of antimicrobials	61 (39%)	148 (31%)	0·05

Data are n (%). Association between the narrowed or discontinued and no change groups was assessed with a χ^2 or Fischer's exact test for sample size greater than ten. LOS=length of stay.

*Narrow spectrum (rank 1), including first-generation and second-generation cephalosporins, amoxicillin, co-trimoxazole, nafcillin, and metronidazole; broad spectrum (rank 2), including fluoroquinolones, extended-spectrum macrolides, third-generation cephalosporins, co-amoxiclav, clindamycin, and oral vancomycin; extended spectrum (rank 3), including antipseudomonal penicillins, cefepime, ertapenem, and intravenous vancomycin; and restricted (rank 4), including antipseudomonal carbapenems, colistin, tigecycline, linezolid, and daptomycin.

Table 3

Factors associated with modifying initial empirical regimens on or before 5th day of therapy and considered for inclusion in the model (p<0·1): escalated versus unchanged

	Escalated (n=88)	Unchanged (n=485)	p value
ICU admission	41 (47%)	167 (34%)	0·03
Abnormal body temperature at start	37 (42%)	151 (31%)	0·05
Relative activity of initial regimen against drug-resistant organisms (rank 1–4) *			0·06
Narrow spectrum (rank 1)	13 (15%)	50 (10%)	
Broad spectrum (rank 2)	44 (50%)	191 (39%)	
Extended spectrum (rank 3)	21 (24%)	179 (37%)	
Restricted (rank 4)	10 (11%)	65 (13%)	
Number of antibiotics			0·02
Monotherapy	61 (69%)	271 (56%)	
2	24 (27%)	178 (37%)	
≥3	3 (3%)	36 (7%)	
Multiple infection sites	19 (22%)	39 (8%)	<0·001
Infection on imaging study done between days 1 and 5	12 (14%)	24 (5%)	0·04
Positive culture from specimen collected between days 1 and 5	9 (10%)	23 (5%)	0·05
Positive culture from specimen collected at start of antimicrobials	41 (47%)	148 (31%)	0·003

Data are n (%). ICU=intensive care unit.

* Narrow spectrum (rank 1), including first-generation and second-generation cephalosporins, amoxicillin, co-trimoxazole, nafcillin, and metronidazole; broad spectrum (rank 2), including fluoroquinolones, extended-spectrum macrolides, third-generation cephalosporins, co-amoxiclav, clindamycin, and oral vancomycin; extended spectrum (rank 3), including antipseudomonal penicillins, cefepime, ertapenem, and intravenous vancomycin; and restricted (rank 4), including antipseudomonal carbapenems, colistin, tigecycline, linezolid, and daptomycin.

Table 4

Multivariable generalised linear latent and mixed model of factors associated with modifications of initial empirical regimen on or before the fifth day of therapy

	Narrowed or discontinued			Escalated		
	Odds ratio	**p value**	**95% CI**	**Odds ratio**	**p value**	**95% CI**
Culture collected at start of antimicrobials	1·68	0·03	1·05–2·70	0·84	0·56	0·48–1·49
Imaging study at start of antimicrobials	0·96	0·87	0·60–3·63	1·69	0·29	0·56–1·64
Spectrum of activity (rank 1–4)	1·32	0·02	1·04–1·67	0·69	0·02	0·52–0·93
Multiple infection sites	1·51	0·18	0·83–2·75	2·54	0·004	1·34–4·83
Positive culture from specimen collected at start of antimicrobials	1·23	0·31	0·82–1·84	1·99	0·007	1·20–3·29
No sign of infection on imaging study done at start of antimicrobials	1·76	0·02	1·11–2·79	1·01	0·98	0·55–1·84

Baseline is patients with unchanged regimens. Spectrum of activity coded as narrow spectrum (rank 1), broad spectrum (rank 2), extended spectrum (rank 3), and restricted (rank 4). There was a 33% increase in the odds of narrowing antibiotics with each 1-unit increase in spectrum of activity.