Recommended antimicrobial therapy for common inpatient infections: a comparative review of guidelines across 51 hospital trusts in England

Daniel Pan [1,2] George Hills,[2] Ashley Ryan Hamilton [2,3] Tamsin Nash,[4] Thomas Hine,[4] Sarah Whitehorn,[4] Gavin Barlow [4]

[1]Department of Respiratory Sciences, University of Leicester, Leicester, UK
[2]Department of Infection and HIV Medicine, University Hospitals of Leicester NHS Trust, Leicester, UK
[3]Leicester School of Pharmacy, De Montfort University, UK, Leicester
[4]Hull York Medical School, John Hughlings Jackson Building, York, UK

Correspondence to
Daniel Pan, NIHR Academic Clinical Fellow in Infectious Diseases, Department of Respiratory Sciences, University of Leicester, Leicester, UK; Daniel.pan@nhs.net

Received 9 June 2020
Revised 21 August 2020
Accepted 30 August 2020
Published Online First 2 October 2020

To cite: Pan D, Hills G, Hamilton AR, *et al*. *Postgrad Med J* 2021;**97**:782–788.

ABSTRACT

Background The number of different antimicrobial recommendations between hospital trusts for the same indication in England is unknown.

Aim We aimed to evaluate the heterogeneity of antimicrobial recommendations for seven common inpatient infections across hospital trusts in England and evaluate changes to recommendations following introduction of national (National Institute for Healthcare and Excellence, NICE) and international (WHO) antimicrobial guidelines.

Methods Guidelines published on the MicroGuide smartphone application were collected from December 2017 to February 2018 and re-evaluated between December 2019 and February 2020. The following indications were assessed: community-acquired pneumonia (CAP) CURB65 score ≥3, hospital-acquired pneumonia (HAP), infective exacerbation of chronic obstructive pulmonary disease (iCOPD), cellulitis, uncomplicated urinary tract infection (uUTI), intra-abdominal infection (IAI) and sepsis of unknown source (SUS). On follow-up, compliance against WHO WATCH antibiotic and NICE recommendations was evaluated.

Results Guidelines were obtained predominantly from England. Antibiotic regimens between hospitals became increasingly diverse across indications in the following order: uUTI, cellulitis, iCOPD, CAP, HAP, IAI and SUS. A piperacillin/tazobactam-based regimen was recommended in HAP (59%), SUS (39%) and IAI (30%). After 2 years, 107 changes were made to 357 antibiotic regimen recommendations; the overall number of regimens using piperacillin–tazobactam and WHO WATCH antibiotics remained similar. Compliance of recommendations with NICE guidelines as follows: iCOPD (100% adherent), uUTI (98%), cellulitis (90%), CAP (43%) and HAP (27%).

Conclusion The heterogeneity of antibiotic recommendations increased as the indicated infection was more severe, with broader underlying bacterial causes. Piperacillin–tazobactam remains favoured in antibiotic regimens, despite not recommended in WHO and NICE guidance.

INTRODUCTION

Antimicrobial resistance (AMR) is a globally important health problem and is partially driven by the excessive use of broad-spectrum antimicrobials in hospitals.[1 2] Restricting their use is difficult, especially in patients presenting with acute, serious infections. Mathematical models have shown that a balanced use of different antimicrobials (heterogeneous antibiotic use) may be another way of reducing the environmental selection pressure that leads to resistance, although this is controversial.[3] Two different strategies for heterogeneous antimicrobial prescribing have been proposed: (1) using different antibiotics during different time periods for the same indication (antibiotic cycling); and (2) promoting diversity of prescription by either forcing prescribers to choose a different antibiotic, or offering a choice between more than one antibiotic, for consecutive patients with the same indication (deliberate and random mixing, respectively).[3]

In the UK, hospital antibiotic guidelines are derived from national or international guidelines, local or national prescribing targets and incentives, such as piperacillin–tazobactam and carbapenem reduction targets,[4] Commissioning for Quality and Innovation (CQUIN) targets, local antimicrobial susceptibility epidemiology and expert opinion. In 2017, the WHO updated the Essential Medicines List[5] and classified key antibiotics into three categories (AWaRe) to improve access (ACCESS group), to monitor important antibiotics (WATCH group) and preserve the effectiveness of 'last resort' antibiotics (RESERVE group). These have been adapted as national CQUIN payment framework targets, as markers of effective stewardship in England.[6] Most recently, the National Institute for Health and Care Excellence (NICE) also published national guidelines, with recommended antimicrobial regimens for common infections.[7] For community-acquired pneumonia (CAP) and uncomplicated urinary tract infection (uUTI), CQUIN performance is based on adherence to NICE guidelines.

While there are local data in the UK on antibiotic consumption and the prevalence of AMR,[8] there is no collated, accessible information about what different hospitals recommend for any given indication, the degree to which antibiotic guidelines differ across hospitals and to what extent, if any, hospitals promote heterogeneous antibiotic use within their guidelines. This project aimed to assess the heterogeneity of antimicrobial recommendations for a selection of common inpatient infections across a sample of hospitals predominantly in England.

METHOD

This was a prospective observational study. MicroGuide (Horizon Strategic Partners) is an

open-access smartphone application that promotes antimicrobial stewardship by providing prescribers access to the antimicrobial guidelines of contributing hospitals.[9] At the time of the study, the tool was used by one-fifth (51/260) of all National Health Service (NHS) hospital trusts in the UK.

Data were collected from all available acute NHS hospital trusts that were using MicroGuide between 1 December 2016 and 28 February 2017. Data were collected for seven common inpatient infections (first-line empiric recommendations only): (1) CAP (CURB65 score ≥3 only); (2) severe hospital-acquired pneumonia (HAP); (3) infective exacerbation of chronic obstructive pulmonary disease (iCOPD); (4) cellulitis; (5) uUTI; (6) intra-abdominal infection (IAI); and (7) sepsis of unknown source (SUS). These indications were chosen because they were infections that every doctor would come across while working in hospital medicine. For indications other than CAP, if recommendations differed by severity, the recommendation for the most severe form of the infection was recorded.

The heterogeneity of antibiotic regimens was assessed and compared across indications within hospitals and within indications between hospitals. For each hospital, the number of different antibiotics and antibiotic classes recommended—all beta-lactams (penicillins, cephalosporins, monobactams and carbapenems) were considered as one class—and the ratio between these was recorded and calculated. The number of combination regimens, regimens without beta-lactams, regimens with piperacillin/tazobactam or a carbapenem, WHO WATCH and RESERVE antibiotics, and regimens with one or more high-risk agent for *Clostridioides difficile* infection were also recorded (high risk was defined as broad-spectrum beta-lactam antibiotics (including broad-spectrum cephalosporins, co-amoxiclav and piperacillin/tazobactam), carbapenems, fluoroquinolones or clindamycin, but excluding temocillin).[10]

Guidelines for the same hospitals were re-reviewed after 3 years (1 December 2019–31 January 2020). Changes recorded included class switching for an indication, to and from beta-lactam regimens; piperacillin/tazobactam and carbapenem regimens; WHO WATCH antibiotic regimens (updated for 2019); high-risk *C. difficile* regimens; as well as NICE recommendations for uUTI, cellulitis, CAP and HAP. Increasing or decreasing the choice of antibiotics for the prescriber as well as switching to and from monotherapy was also recorded.

Continuous variables are expressed as medians and IQRs. Categorical variables are expressed as numbers and percentages (%). The Kruskal-Wallis test was used to compare continuous variables between groups. Fisher's exact test was used to compare categorical variables between groups. Statistical analysis was performed using STATA version 14.2 (StataCorp, Texas, USA) and Excel version 2016 (Microsoft, Redmond, USA).

RESULTS

For the seven studied indications, 357 antibiotic recommendations in 51 trusts were identified. Twenty-one (41%) of the trusts were teaching hospitals. Apart from one trust in Wales, all trusts were in England with the majority (38, 75%) situated in the south-west of England (figure 1).

The most commonly recommended antimicrobial regimens from December 2016 to February 2017 are shown in table 1. Co-amoxiclav and a macrolide were favoured by over one-third of trusts for CAP; piperacillin/tazobactam was recommended for HAP by one-half of all hospitals. Flucloxacillin monotherapy was the most commonly recommended antibiotic for cellulitis, while nitrofurantoin monotherapy was the most commonly recommended antibiotic for uUTI.

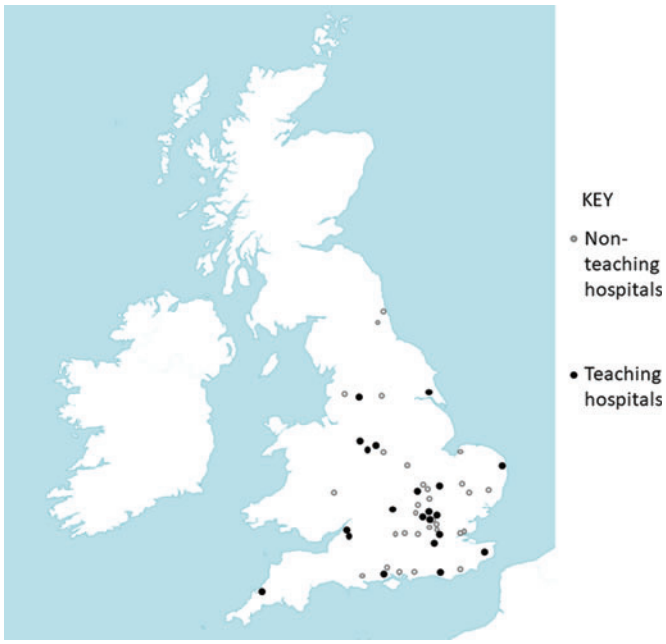

Figure 1 Geographical distribution of trusts included in the study.

Table 1 Top three recommended antibiotic regimens for each inpatient indication

Diagnosis	Top three antibiotic regimens recommended	% of all hospitals (N=51)
CAP (CURB65 score ≤3 only)	Co-amoxiclav+macrolide	41
	Benzylpenicillin or amoxicillin+macrolide	37
	Benzylpenicillin or amoxicillin+macrolide or doxycycline	8
HAP	Piperacillin–tazobactam	53
	Co-amoxiclav	12
	Amoxicillin+temocillin	6
iCOPD	Amoxicillin	41
	Doxycycline	35
	Amoxicillin or doxycycline	10
Cellulitis	Flucloxacillin	63
	Flucloxacillin+benzylpenicillin	25
	Flucloxacillin or benzylpenicillin+clindamycin	12
uUTI	Nitrofurantoin	41
	Nitrofurantoin or trimethoprim	33
	Trimethoprim	18
IAI	Piperacillin–tazobactam	22
	Amoxicillin+gentamicin+metronidazole	20
	Co-amoxiclav	20
SUS	Co-amoxiclav+entamicin	23
	Piperacillin–tazobactam	20
	Piperacillin–tazobactam+gentamicin	14

CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; CURB65 score, pneumonia severity score; HAP, hospital-acquired pneumonia; IAI, lintra-abdominal infection; iCOPD, infective exacerbation of COPD; SUS, Sepsis of unknown source; uUTI, uncomplicated urinary tract infection.

Excluding uUTI, across indications, a large proportion of hospitals (60–100%) recommended a first-line antibiotic regimen containing a beta-lactam (see figure 2). Combination therapy using more than one class was commonly recommended for CAP (100%), SUS (70%) and IAI (55%). Few hospitals offered clinicians a choice between antibiotics or antibiotic classes, except for uncomplicated uUTI where 41% of hospitals offered a choice, mostly between nitrofurantoin or trimethoprim, and iCOPD where 22% of hospitals offered a choice, most commonly

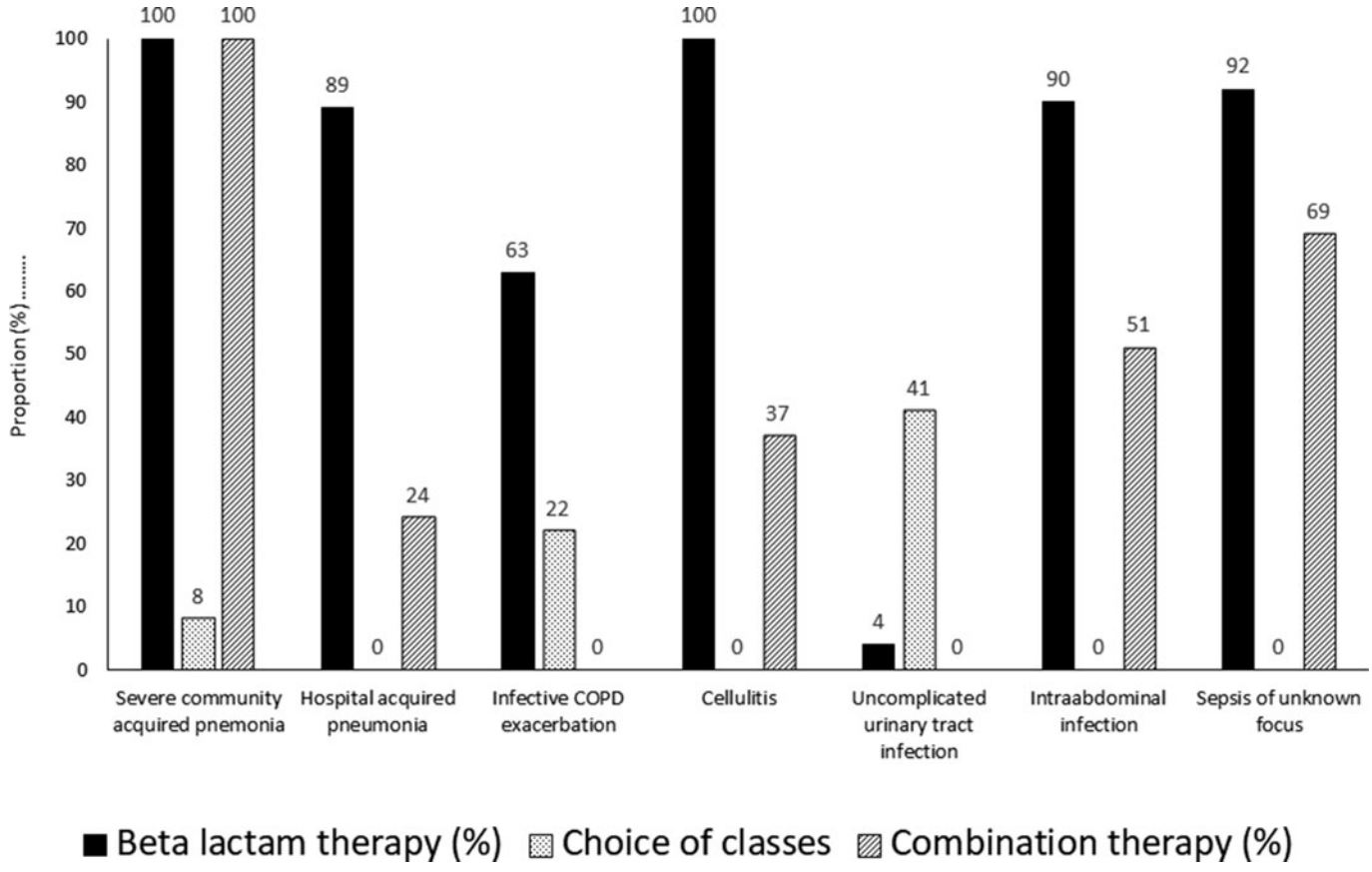

Figure 2 Proportion of trusts recommending beta-lactam therapy, offering the prescriber a choice of different antibiotic classes (with beta-lactams considered as one class) and recommending combination therapy. Combination therapy simply means recommending two or more antibiotic classes instead of one. COPD, chronic obstructive pulmonary disease.

between amoxicillin and doxycycline. No hospitals offered clinicians a choice between antibiotic classes for HAP, cellulitis, IAI or SUS.

Figure 3 illustrates the heterogeneity of antimicrobial regimens recommended across trusts for each infection, from December 2016 to February 2017. There appeared to be a broad qualitative relationship (not statistically assessed) between an increasing severity of the indication and increased the heterogeneity antibiotic regimen across hospitals (figure 2).

More than half of hospitals (58%) recommended 8–10 different antibiotics for the seven indications studied, with 55% recommending five or six different classes (beta-lactams considered as one class) (table 2). The median (IQR) number of beta-lactam containing and combination regimens recommended across the seven indications by hospitals was 6 (IQR 5–6) and 3 (2–4), respectively. Carbapenems were not recommended as first-line empiric therapy for any indication in any hospital, but piperacillin/tazobactam was commonly recommended first-line for HAP (59%), SUS (39%) and IAI (30%).

No hospital recommended any of the WHO RESERVE antibiotics as first-line therapy. Across hospitals and recommendations, a WHO WATCH antibiotic was identified in 83 (23%) of all recommendations; mostly (95%) for HAP, IAI or SUS and mostly piperacillin–tazobactam (82% of all WATCH antibiotics recommended, 19% of total recommendations). WHO WATCH antibiotics were more commonly prescribed in non-teaching versus teaching hospitals as shown in table 2. Cephalosporins or fluoroquinolones were rarely suggested (3% of all recommendations). However, 68% of hospitals recommended a high-risk antibiotic for *C. difficile* infection for three or more of the seven indications (mostly co-amoxiclav or piperacillin/tazobactam).

Re-review of recommendations in 2019/2020

On follow-up, almost one-third of recommendations (107/357, 30%) had been changed. Excluding cellulitis and uUTI, where most regimens were changed to flucloxacillin and nitrofurantoin monotherapy, other changes did not appear to be systematic and appeared to be specific to each hospital (table 3). The overall recommendation of beta-lactams, piperacillin/tazobactam and WHO WATCH antibiotics remained similar in the two periods. Compliance with NICE recommendations for iCOPD, cellulitis and uUTI was high compared to CAP and HAP (table 4). Three guidelines (6%) defined HAP differently (≥3–4 days) compared to NICE guidance (≥48 hours).

DISCUSSION

We present a baseline summary of antibiotic recommendations in a selection of predominantly English hospitals during which national NICE and international WHO antibiotic guidelines were published (December 2016–February 2020). We found a considerable heterogeneity of recommended antibiotic regimens across hospitals and that over a 4-year follow-up period; this heterogeneity was retained with little overall change in antibiotic recommendation characteristics.

The heterogeneity of recommended antibiotic regimens appeared to be related to the severity of the suspected indication and spectrum of potential underlying bacterial causes. There was

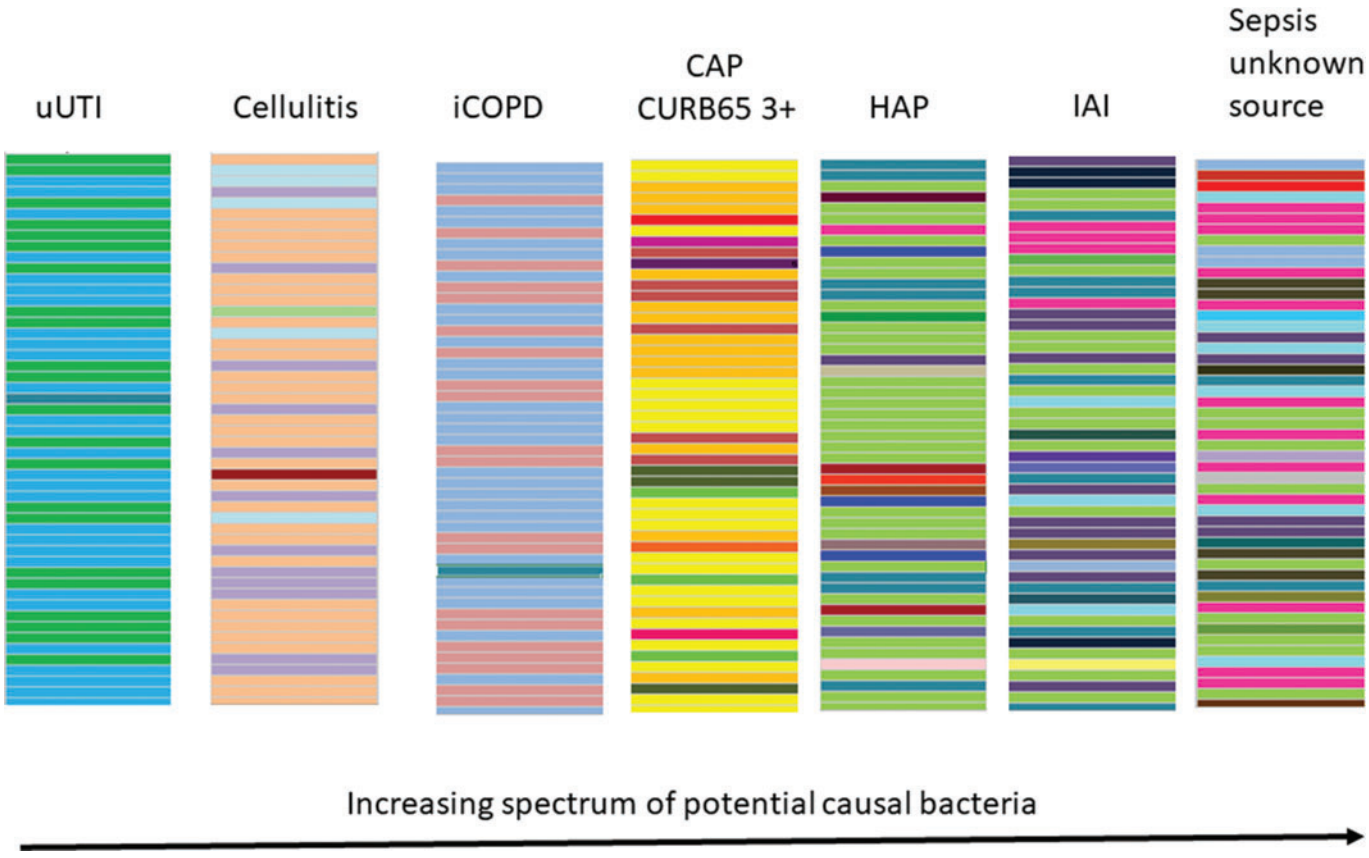

Figure 3 Heterogeneity of antibiotic recommendations across hospital trusts for common inpatient infections. Each colour recommends a different antibiotic regimen. CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; CURB65 score, pneumonia severity score; HAP, hospital-acquired pneumonia; IAI, intra-abdominal infection; iCOPD, infective exacerbation of COPD; uUTI, uncomplicated urinary tract infection.

Table 2 Indices for the seven indications studied, separated by whether the trust included a teaching hospital or not

Indices for the seven indications studied	Median (IQR)	Range	% of hospitals above/below median	Teaching hospital—median (IQR)	Non-teaching hospital—median (IQR)	P value
Number of different antibiotics	8 (7–9)	5–10	33% above 42% below	8 (6–9)	8 (7–9)	0.45
Number of different antibiotic classes	5 (4–5)	3–6	22% above 45% below	5 (4–5)	5 (4–5)	0.56
Number of different antibiotics/number of different classes	1.6 (1.5–2)	NA	NA	1.6 (1.5–1.8)	1.6 (1.5–2)	0.88
Number of combination regimens	3 (2–4)	1–5	31% above 40% below	3 (2–4)	3 (2–4)	0.54
Number of regimens with one or more beta-lactam	6 (5–6)	3–7	2% above 49% below	6 (5–6)	6 (5–6)	0.87
Number of regimens with Piperacillin–tazobactam or a carbapenem	1 (1–2)	0–4	46% above 24% below	1 (0–1)	2 (1–3)	0.06
Number of regimens with WHO WATCH antibiotic (2017)	3 (2–3)	0–4	24% above 47% below	2 (1–3)	3 (2–4)	0.05
Number of regimens with one or more high-risk *Clostridioides difficile* agents	3 (2–4)	0–5	41% above 32% below	3 (2–4)	4 (2–4)	0.14

more consistency of recommendations across hospitals for less severe infections (cellulitis, uUTI and iCOPD) that have a more predictable and narrower spectrum of causal pathogens, compared to CAP, HAP, IAI and SUS for which a wider range of antibiotic recommendations was offered. This may be due to the considerable documented geographic variation in levels of AMR, particularly for gram-negatives, as well as variation in the opinions of local infection teams in the absence of high-quality evidence.

Conversely, random antibiotic mixing (offering the prescriber a choice of antibiotics for a specific indication) and monotherapy were predominantly offered for infections of lower severity (cellulitis, uUTI and iCOPD). Recommendations for the less severe infections were also more likely to adhere to NICE guidelines on follow-up. Interestingly, the much lower adherence with NICE recommendations for CAP and HAP may suggest a lack of confidence in NICE guidelines for these indications within local infection teams. Clarithromycin, recommended by NICE for

Table 3 Top three antibiotic changes in December 2019–February 2020 compared to December 2017–February 2018

Diagnosis	Three most common antibiotic changes within an antibiotic regimen (WHO WATCH antibiotic are in italics)	NICE-recommended regimen (WHO WATCH antibiotic are in italics)	Number of changes (% of trusts changing) N=107
CAP	Total number of changes	Co-amoxiclav and *clarithromycin*	21 (41)
	Clarithromycin to doxycycline		6 (12)
	Benzylpenicillin to co-amoxiclav		3 (6)
	Clarithromycin to *azithromycin*		2 (4)
HAP	Total number of changes	Co-amoxiclav	12 (24)
	Piperacillin–-tazobactam to co-amoxiclav		5 (10)
iCOPD	Total number of changes	Amoxicillin or doxycycline or *clarithromycin*	15 (30)
	Doxycycline or *clarithromycin* to amoxicillin		3 (6)
	Doxycycline to amoxicillin or doxycycline or *clarithromycin*		3 (6)
	Doxycycline to doxycycline or *clarithromycin*		2 (4)
Cellulitis	Total number of changes	Flucloxacillin	9 (18)
	Flucloxacillin and benzylpenicillin to flucloxacillin		5 (10)
uUTI	Total number of changes	Nitrofurantoin	20 (39)
	Trimethoprim to nitrofurantoin		8 (16)
	Trimethoprim or nitrofurantoin to nitrofurantoin		6 (12)
	Trimethoprim to trimethoprim or nitrofurantoin		2 (4)
uIAI	Total number of changes	NA	15 (30)
	Piperacillin–tazobactam to co-amoxiclav		2 (4)
SUS	Total number of changes	NA	15 (30)
	Switched to no guidance		2 (4)
	Piperacillin–tazobactam to co-amoxiclav		2 (4)
	Amoxicillin to co-amoxiclav		2 (4)

Only the three most common antibiotic changes within an antibiotic regimen are shown. For HAP, cellulitis and uIAI, only one change is shown because all other changes in regimens did not occur in more than one trust, that is, high heterogeneity.
CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; HAP, hospital-acquired pneumonia; IAI, intra-abdominal infection; iCOPD, infective exacerbation of COPD; SUS, Ssepsis of unknown source; uUTI, uncomplicated urinary tract infection; NA.

Table 4 Changes to guidelines in December 2019–February 2020 compared to December 2016–February 2017

	CAP	HAP	iCOPD	Cellulitis	uUTI	IAI	SUS	Total antibiotic changes N=357 (%)
Change of one antibiotic								
Different antibiotic, same class	9	3	2	7	0	4	6	31 (9%)
Different class of antibiotic	11	4	9	1	10	3	0	38 (11%)
Beta lactam (from a different class)								
Switched to	0	2	5	0	0	0	0	5 (1%)
Switched from	0	2	0	0	0	0	0	
Piperacillin/tazobactam								
Switched to	0	2	1	1	0	1	2	11 (3%)
Switched from	2	8	0	0	0	4	4	
WHO WATCH antibiotics (2019)								
Switched to	4	3	8	1	0	2	4	5 (1%)
Switched from	0	8	1	0	0	7	1	
NICE recommendations								
Switched to	5	5	6	6	14	NA	NA	23 (6%)
Switched from	11	0	2	0	0	NA	NA	
High-risk *C. difficile* agent (from a lower-risk *C. difficile* agent)								
Switched to	0	2	6	0	0	4	4	11 (3%)
Switched from	0	1	0	0	0	3	1	
Offering a choice of antibiotics								
Increased choice	0	0	9	0	2	6	4	2 (1%)
Decreased choice	1	0	2	7	6	4	3	
Monotherapy								
Switched to	1	1	2	6	6	2	1	4 (1%)
Switched from	0	2	9	0	2	6	4	
Total number of hospitals adhering to NICE recommendations	22 (43%)	14 (27%)	51 (100%)	46 (90%)	50 (98%)	NA	NA	NA

The total antibiotic changes is the total number of antibiotic changes of the same type, made across all 51 guidelines.
C. difficile, *Clostridioides difficile*; CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; HAP, hospital-acquired pneumonia; IAI, iintra-abdominal infection; iCOPD, infective exacerbation of COPD; NICE, National Institute for Health and Care Excellence; SUS, sepsis of unknown source; uUTI, uncomplicated urinary tract infection.

CAP or iCOPD, is also a WHO WATCH antibiotic (table 3). This may be worthy of further investigation prior to any future iterations of these national guidelines.

Formal antibiotic cycling within hospitals was challenging to capture since no guideline specifically stated that the regimen recommended was part of an alternating cycle. However, most changes to antibiotic regimens on follow-up did not result in a net change in important indicators of stewardship, such as beta-lactam containing regimens or WHO WATCH antibiotics. We found no evidence that any hospital was following a cycling approach for the indications studied.

We found that a relatively high proportion of trusts continued to recommend regimens containing piperacillin/tazobactam (almost one in five of all recommendations) even with national incentives for use reduction in place at the time of initial data collection.[4] This proportion was higher in non-teaching hospital trusts and did not change significantly over 4 years, even with the introduction of national and international guidelines. It seems that many infection teams in the UK continue to favour broad-based antibiotic regimens containing a beta-lactam (most commonly piperacillin/tazobactam) for severe infections. In these cases, piperacillin/tazobactam may be favoured due to familiarity, availability and its anti-pseudomonal properties. Although they continue to be effective, there are emerging alternatives, such as cephalosporins and monobactams. High-quality data for the use of these novel antibiotics compared with piperacillin–tazobactam, as well as assessment of combination therapy for severe *Pseudomonas* infection, continue to be lacking and novel technologies that involve therapeutic drug monitoring are not yet widely available, especially in district general hospitals.

It is possible recommendations in the future may be influenced by the results of the MERINO trial (Harris and colleagues) which showed that piperacillin/tazobactam was inferior to meropenem for the treatment of ceftriaxone-resistant *Escherichia coli* or *Klebsiella pneumoniae* bacteraemia.[11] In the context of empirical antimicrobial prescribing, when organism sensitivities are not known, this study may influence guidelines in hospitals with a high prevalence of resistant gram-negative infections. Whether other carbapenem sparing regimens, such as those including an aminoglycoside, temocillin or aztreonam, which are likely to be preferred to carbapenems by UK hospital infection teams, are also inferior to meropenem is unknown.

Spyridis and colleagues also found considerable variation across 84 paediatric hospital antibiotic guidelines in Europe.[12] Our findings are consistent with the well-described and known variation in antibiotic use within local and international settings.[13] Currently, there are no published data on variation in microbial resistance across local trusts in England. Why such variation in guidelines exists across trusts in England is unknown, but local microbial resistance epidemiology is unlikely to be solely responsible, particularly when trust catchment areas often overlap. The patient population which a hospital serves may have an influence on the antibiotics recommended—for example, university hospitals are tertiary referral centres for many specialities, and therefore may have more complex patients, higher healthcare exposure and greater risks of acquiring resistant organisms, thus resulting in further diversity in prescribing.

To fully understand antibiotic prescribing and resistance in the UK, it is important to link local antibiotic guideline recommendations with actual prescribing and microbial epidemiology. For example, how do local guideline recommendations influence local prescribing and microbial epidemiology, and how can guidelines be used to positively influence AMR? These relationships remain unclear, although future work could involve creation of a national antibiotic guideline database that could then be linked to local antimicrobial use and resistance prevalence data for key pathogens. Such a database might help coordinate necessary and rapid changes in local antibiotic recommendations in response to emerging AMR problems, improve consistency in the definition of infections and facilitate the study of the heterogeneity of antibiotic recommendations on the emergence of AMR. Importantly, the database may help to clarify the possible benefits of heterogeneic antimicrobial prescribing.

Limitations

Our study has several limitations. The number of trusts using MicroGuide as well as other platforms have since increased since the start of our study. While a larger national survey may be useful, using MicroGuide allows for minimisation of lost to follow-up and allows us to track changes in antimicrobial recommendations over time. Most of the trust guidelines were concentrated in England, and especially in the South of England; our findings do not necessarily represent antibiotic guidelines in Scotland or Wales. For pragmatism, only first-line recommendations for the seven indications were included; examination of recommendations for those allergic to penicillin or other agents, duration of therapy or the treatment of resistant infections might be of interest. We also did not explore other common inpatient infections, such as complicated UTIs. Nevertheless, our study provides a useful baseline summary of antimicrobial recommendations across England from December 2016 to February 2020.

Main messages

- What is already known about the subject: Strategies to diversify antibiotic prescribing for one indication may help to slow down antimicrobial resistance.
- There is considerable heterogeneity of recommended antibiotic regimens across hospitals in England for common inpatient bacterial infections.
- There is more heterogeneity in recommendations for the more severe infections with broader underlying bacterial causes.
- Over a 4-year follow-up period, this heterogeneity was retained with relatively little overall change in antibiotic recommendation characteristics.
- Piperacillin–tazobactam remains a favoured antibiotic recommendation for severe broad-spectrum infections, despite national incentives at the time of study to decrease its use.
- Recommendations in general offered the prescriber little choice for specific indications, although the offer of a choice was more common for uncomplicated UTI and infective exacerbations of COPD.

Current research questions

- What are the factors that influence local hospital antimicrobial recommendations to adhere to national guidance, such as NICE?
- Why do the majority of UK hospital guidelines for common inpatient infections favour the use of piperacillin–tazobactam, despite national incentives to decrease its use at the time of study?
- Why is there such variation in antibiotic recommendations across different trusts for the same indication?
- Can heterogenic strategies of antimicrobial use for one indication influence antimicrobial resistance?

Twitter Ashley Hamilton @RyanPharmilton.

Acknowledgements The authors would like to thank the developers of MicroGuide without which this study would not be possible.

Contributors DP and GB devised the study. DP, GH, ARH, TN, TH and SW collected and analysed the data. DP and GB drafted the first version of the manuscript. All authors contributed to the final version of the manuscript. DP is responsible for the overall content as guarantor.

Funding DP is funded by the National Institute for Health Research.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open-access repository. Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplemental information.

ORCID iDs
Daniel Pan http://orcid.org/0000-0002-1268-2243
Ashley Ryan Hamilton http://orcid.org/0000-0002-9328-2398
Gavin Barlow http://orcid.org/0000-0002-4018-6685

REFERENCES

1 The World Health Organization. *Global action plan on antimicrobial resistance*. World Health Organization 2015.
2 Chatterjee A, Modarai M, Naylor NR, *et al.* Quantifying drivers of antibiotic resistance in humans: a systematic review. *Lancet Infect Dis* 2018;3099:1–11.
3 Beardmore RE, Peña-Miller R, Gori F, *et al.* Antibiotic cycling and antibiotic mixing: which one best mitigates antibiotic resistance? *Mol Biol Evol* 2017;34:802–17.
4 Public Health England. English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report 2017. *Public Heal Engl* 2017:1–143.
5 WHO. 20th edition WHO model list of essential medicines (March 2017). *Essent Med Heal Prod* 2017:1–39.
6 NHS England. Reducing the impact of serious infections CQUIN 2018/19 FAQs, parts 2c and 2d. 2018: 1–6.
7 The National Institute for Health and Care Excellence (NICE) and Public Health England (PHE). Summary of antimicrobial prescribing guidance - managing common infections. 2019: 1–23.
8 Public Health England. English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) Report 2018.
9 Fleming A, Tonna A, O'Connor S, *et al.* Antimicrobial stewardship activities in hospitals in Ireland and the United Kingdom: a comparison of two national surveys. *Int J Clin Pharm*.
10 Lawes T, Lopez-Lozano JM, Nebot CA, *et al.* Effect of a national 4C antibiotic stewardship intervention on the clinical and molecular epidemiology of Clostridium difficile infections in a region of Scotland: a non-linear time-series analysis. *Lancet Infect Dis* 2017;17:194–206.
11 Harris PNA, Tambyah PA, Lye DC, *et al.* Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with E coli or Klebsiella pneumoniae bloodstream infection and ceftriaxone resistance. *JAMA* 2018;320:984–94.
12 Spyridis N, Syridou G, Goossens H, *et al.* Variation in paediatric hospital antibiotic guidelines in Europe. *Arch Dis Child* 2016;101:72–6.
13 Zanichelli V, Monnier AA, Gyssens IC, *et al.* Variation in antibiotic use among and within different settings: a systematic review. *J Antimicrob Chemother* 2018;73:17–29.