Supplementary material.
The UKHSA antibiotic assessment tool.
Adapted from The UKHSA (formerly PHE) tool available via Hood et al. Measuring Appropriate Antibiotic Prescribing in Acute Hospitals: Development of a National Audit Tool Through a Delphi Consensus. Antibiotics (Basel) 2019;8(2).

ANTIBIOTIC APPROPRIATENESS – END OF COURSE ASSESSMENT – DRAFT v8.1_np
Survey to be performed for a <u>single</u> episode of infection in hospitalised ADULTS at the end of a course of therapy (or if stop-date confirmed)
IMPORTANT: data fields are optional and designed to support decision-making overleaf

DEMOGRAPHICS			
Survey number:		Hospital number:	
Survey date:		Admission date:	Discharge date:
Your name:		Age:	
Your profession:		Gender:	
Infection specialist:		Ward:	
Data collection time:	mins	Hospital specialty:	

MEDICAL CASE NOTES	
Presenting complaint:	
History of presenting complaint:	
Relevant past medical history:	
Immunocompromised?†	no
Relevant family or social history:	
Relevant drug history:	
Allergy to antibiotics:	
Urine dipstick test result:	
Evidence of infection at anatomical site?	
Details of evidence of infection from systems review and examination:	
WORKING infection diagnosis:	
Progress notes over next 2-3 days: stroke	
Review of antibiotic prescription within 72h?	Y / N / Uncertain
Prescribing decision at pre-72h review:	

LABORATORY RESULTS (include date)			
Record most significant laboratory results **before starting antibiotics** & during therapy	Pre-start	Day 2-3	Day 5-7
C-Reactive Protein (CRP):			
White Blood Cell (WBC) count:			
Lactate:			
Other relevant laboratory results:			

MICROBIOLOGY	
Blood cultures: Y / N	Pathogen identified: Y / N
Other specimen cultures: Y / N	Pathogen identified: Y / N
Has there been a discussion with Medical Microbiology?	
Details (include date, specimen type, pathogen ID, susceptibilities):	

MEDICAL IMAGING
Details (include date, imaging modality, findings):

Vital Signs & National Early Warning Score (NEWS-2)			
Physiological Parameters	**Pre-start**	**Day 3**	**Day 5-7**
Respiration Rate (per minute)			
SpO_2 (%)			
Air or oxygen?			
BP (mmHg)			

FINALISED infection diagnosis:	
Local standard course length for infection:	days
Explanation for prolonged antibiotic course?	

Pulse (per minute)	
Consciousness (ACVPU)	
Temperature (°C)	
NEWS-2 Score:	

†**Definition of immunocompromised** consistent with the "Green Book". i.e. Any of: Immunodeficiency syndrome; HIV infection; Bone marrow or stem cell transplant; Chemo / radiotherapy within 6 months; High-dose steroids >/=40mg prednisolone/day for >7days; or Immunosuppressant drugs.

Infection specialist judgment of appropriateness of antibiotic prescribing		If "No", document explanation and estimate excess days of therapy in the table below	
A. Was antibiotic treatment indicated from the outset? i.e. Was it reasonable to start antibiotic treatment under the circumstances? • Consider only the information available to the prescriber at the time of prescribing (e.g. symptoms/signs; vital signs; laboratory results; urine dipstick; near-patient tests; microbiology; imaging) • Do not take antibiotic spectrum into consideration; judge only whether any antibiotic was indicated	Y	Comments:	Specialty & consultant name
B. Was antibiotic treatment indicated beyond the post-prescription (48-72h) review? i.e. Was it reasonable to continue antibiotics beyond 72 hours? • Consider only the information available to the prescriber at the time of the post-prescription review (e.g. symptoms/signs; vital signs; laboratory results; microbiology; imaging)	N		Specialty & consultant name
C. Was antibiotic treatment indicated beyond the standard treatment duration for the infection? i.e. Was it reasonable to continue antibiotics beyond the standard course length in local guidelines? • Document any explanation for prolonged treatment (e.g. persistent symptoms, uncontrolled source)	n		Specialty & consultant name

DRUG CHART / PRESCRIPTION						**Record any non-essential (excess) days of therapy (DOTs) for one of 3 reasons**		
Antibiotic	**Drug name (route & dose regimen)**	**Start date* & time**	**Stop date* & time**	**Days of therapy (DOTs)¥**	**Comments**	A. Antibiotic(s) not indicated at outset	B. Unexplained continuation beyond 72 hours	C. Unexplained continuation beyond standard duration
1				days		days	days	days

2	days		days	days	days
3	days		days	days	days
4	days		days	days	days
5	days		days	days	days
6	days		days	days	days
7	days		days	days	days

¥The international definition of a DOT is any day on which one or more doses of antibiotic are administered		Total days of non-essential antibiotic therapy	Days*	Days*	Days*
Total DOTs (sum of all antibiotics)	days	**GRAND TOTAL non-essential antibiotic DOTs (sum of A + B + C)**			Days*
COURSE LENGTH (earliest start date to final stop date)	days				

EXPLANATORY NOTES FOR DATA COLLECTORS

Survey of Appropriateness of Antibiotic Therapy for a Single Episode of infection in Adult Patients in an Acute Hospital Setting – DRAFT v8.1

Aim

This survey aims to estimate what proportion of antibiotic (antibacterial) days of therapy are non-essential in the judgement of the reviewer and therefore potentially avoidable.

Rationale

The focus on avoidable days of therapy is deliberate; to establish whether there is room for improvement in antibiotic consumption and to identify improvement goals that are safe for patients and relevant for antibiotic resistance. Assessment of appropriateness is subjective but this survey aims to standardise the assessment as much as possible by prompting the collection of relevant information to allow an infection specialist (doctor or pharmacist) to evaluate the appropriateness of antibiotic prescribing in a consistent way. *This survey instrument is <u>not</u> designed to capture information on off-guideline prescribing or overuse of broad-spectrum or IV antibiotics, nor is the survey designed to evaluate peri-operative surgical prophylaxis.*

Method

Selecting patients for the survey is critical. Please include adult patients at the end, or nearing the known end, of a course of treatment for a single episode of infection (completing treatment courses on the ward with a stop date or on discharge prescriptions). Seek the co-operation of ward pharmacists or dispensary staff (for discharge prescriptions) to identify patients at the end of a course of antibiotics, or use your e-prescribing system. Aim to sample randomly across a range of medical and surgical specialties. A sample of 50-100 patients per hospital is required to obtain a reliable estimate of the appropriateness of prescribing overall for your hospital.

Data for submission to survey organisers

Data items for submission are indicated with an asterisk. This is a minimum dataset to reduce workload associated with this survey. The majority of data items included in this survey instrument are for the benefit of the expert when estimating appropriateness and to allow the survey team to maintain a record of the source patient and date.

NEWS-2

For patients with no apparent evidence of local infection at an anatomical site, NEWS-2 is provided as an aid for identifying sepsis of uncertain origin and also to capture apparent discordance between clinical findings and prescribing behaviour. *This score has not been validated in paediatric patients.*

Applying NEWS ≥3 as a screening threshold for severe sepsis (Surviving Sepsis Campaign 2012 criteria) had sensitivity of 93% and a negative predictive value of 99.5% in an Emergency Department (ED) setting in London [Keep JW et al, 2016]. A study of over 27,000 adult patients admitted to 20 Scottish hospitals identified almost 20% meeting the Surviving Sepsis Campaign 2012 criteria for sepsis; only 9.7% of these patients had a NEWS <3 before leaving the ED [Corfield AR et al, 2014]. In December 2017, the Royal College of Physicians updated NEWS to NEWS-2 with a threshold of ≥5 for consideration of sepsis. [RCP 2017]

National Early Warning Score (NEWS2)							
PHYSIOLOGICAL PARAMETERS	**3**	**2**	**1**	**0**	**1**	**2**	**3**
Respiration Rate (per minute)	≤8		9-11	12-20		21-24	≥25
SpO_2 Scale 1§ (%)	≤91	92-93	94-95	≥96			
SpO_2 Scale 2§ (%)	≤83	84-85	86-87	88-92 or ≥93 on air	93-94 on oxygen	95-96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
BP systolic (mmHg)	≤90	91-100	101-110	111-219			≥220

Pulse (per minute)	≤40		41-50	51-90	91-110	111-130	≥131
Consciousness (ACVPU)				A			C, V, P, or U
Temperature (°C)	≤35.0		35.1-36.0	36.1-38.0	38.1-39.0	≥39.1	
TOTAL SCORE							

§Use Scale 2 if target range is 88–92%, e.g. in hypercapnic (Type 2) respiratory failure (usually due to COPD).
ACVPU = Alert; new-onset Confusion, disorientation and/or agitation; responds to Voice; responds to Pain; Unresponsive

Royal College of Physicians. National Early Warning Score (NEWS) 2: Standardising the assessment of acute-illness severity in the NHS. London: RCP, 2017.
"A NEW score of 5 or more in patients with a known infection, signs or symptoms of infection, or at high risk of infection, is most likely to represent sepsis requiring a rapid escalation of clinical care, confirmatory investigations and urgent treatment." RCP 2017

SECTION II – ASSESSMENT OF APPROPRIATENESS OF *INTRAVENOUS ROUTE*			
Exclusion criteria		**IV-to-oral Switch Criteria**	**Date when criterion met**
Staph. aureus bacteraemia	Y / N	24 hours of IV therapy complete	
Meningitis or CNS infection	Y / N	Afebrile (<38˚C) for >24 hours	
Abscess or empyema (undrained)	Y / N	Clinical condition improving	
Haematological malignancy or neutropenia	Y / N	Haemodynamically stable	
Legionella pneumonia	Y / N	CRP trending towards normal	
Osteomyelitis or mediastinitis	Y / N	WBC trending towards normal	
Septic arthritis	Y / N	Able to tolerate oral medication	
Prosthetic device or foreign body infection	Y / N	Functioning GI tract without risk of malabsorption	
Necrotising fasciitis or other severe soft tissue infection	Y / N	**Date when ALL criteria met:**	
Endocarditis or intravascular infection	Y / N	Appropriate oral antibiotic available	Y / N
Cystic Fibrosis exacerbation	Y / N		
Haematological malignancy or neutropenia	Y / N		**Reference: Mertz D *et al*, 2009**

DRUG CHART / PRESCRIPTION						Record any non-essential (excess) IV route days of therapy (DOTs) for one of 3 reasons		
Antibiotic	**Intravenous antibiotic (IVAb) name (route & dose regimen)**	**Start date & time**	**Stop date & time**	**Days of therapy (DOTs)¥**	**Date & time IV-to-oral switch criteria met (enter N/A if switch criteria not met)**	A. IVAb(s) not indicated at outset (oral route appropriate)	B. Unexplained continuation beyond switch date	C. Unexplained continuation beyond standard course length for infection
1				days		days	days	days
2				days		days	days	days
3				days		days	days	days
4				days		days	days	days
5				days		days	days	days
¥The international definition of a DOT is any day on which one or more doses of antibiotic are administered					Total days of non-essential IV route antibiotic therapy	Days*	Days*	Days*
Total DOTs (sum of all IV route antibiotics)				days	**GRAND TOTAL non-essential IV antibiotic DOTs (sum of A + B + C)**			Days*

DEFINING AND MEASURING "APPROPRIATE" ANTIBIOTIC PRESCRIBING – A BRIEFING FOR AUDITORS

Dr Kieran Hand, Consultant Pharmacist – Anti-infectives, University Hospital Southampton NHS Foundation Trust. 26 September 2017.

Background

The UK government has pledged to reduce inappropriate antibiotic prescribing by 50% by the year 2020.a

a https://www.gov.uk/government/speeches/g7-2016-in-japan-pm-press-statement

Antimicrobial therapy and prophylaxis in hospitals has been reported to be incorrect or not indicated in 9-64% of cases and this variation is partly explained by differences in applied definitions of appropriateness as well as differences in subjective judgment of auditors.[1,2] Antibiotic prescribing in the absence of infection is likely to be less of a problem in secondary care compared to primary care but nonetheless has been reported to range from 9.3% in Wales (Wrexham) to 50% in Scotland (Aberdeen).[1,3-9] A recent six-hospital study from the US reported that at the time of starting antimicrobials, one third of patients did not have a fever or abnormal WBC count, and half of the requested radiology and microbiology results did not identify an infection.[9] This suggests that a large proportion of antibiotic use could have been avoided.

Variability in subjective judgment of appropriateness by infection experts is acknowledged in studies reporting inter-rater reliability.[10] ID physicians are reported to disagree on appropriate antibiotic therapy 30% of the time.[11]

The purpose of this document is to introduce an audit tool that has been drafted in an attempt to standardise the process of auditing appropriateness of antibiotic prescribing in NHS hospitals in order to quantify the degree of inappropriate prescribing and define the goal of reducing this by 50%.

Establishing prescribing standards & defining appropriateness

Defining the gold standard for appropriate antibiotic prescribing is a subjective process and a list was compiled to incorporate those elements of high-quality prescribing identified by opinion leaders in the field such as Dr Inge Gyssens,[12-14] government advisory committees such as APRHAI,[15,16] and panels of experts convened for the purpose of defining appropriate prescribing.[17] The table below (Table 1) sets out many of the elements of antibiotic prescribing that may be considered in an assessment of appropriateness. The elements are structured within the "Start Smart, Then Focus" format.[15]

It could reasonably be argued that each of these elements is relevant to improving patient outcomes and critical to the assessment of appropriateness of prescribing. However, APRHAI took a view that improvement in performance against certain elements would not impact upon the overall consumption of antibiotics and, consequently, would be less likely to impact upon antibiotic resistance. Three aspects were therefore given **ultimate priority** as most relevant to resistance and presented to APRHAI as follows:

"For the purpose of delivering the ambition of halving inappropriate prescribing in the UK, inappropriate prescribing is defined as;

- Prescribing an antibiotic for a patient in the absence of (documented) evidence of bacterial infection.
- Prescribing a critical broad-spectrum antibiotic (piperacillin-tazobactam or carbapenems in secondary care; co-amoxiclav, cephalosporins and quinolones in primary care) to patients in the absence of a (documented) rationale.
- Continuing an antibiotic prescription beyond the course length recommended in local or national guidelines, in the absence of a (documented) rationale."

A key function of the draft audit tool is to estimate the number of days of antibiotic therapy that auditors consider non-essential and therefore potentially avoidable. This will allow the NHS to set goals for reduction of antibiotic consumption in hospitals that are safe and achievable. **Table 1. Elements of antibiotic prescribing in hospitals relevant for evaluating appropriateness**[12-17]

Prescribing elements (potential audit standards)	**Comments**	**Selected for audit**
START SMART		
No antibiotic if not indicated (no reasonable evidence of infection)	Unnecessary antibiotic exposure selects for avoidable resistance.[18-20]	✓
Indication documented	Good practice for continuity of care but of uncertain relevance to resistance.	✓
Appropriate specimens taken for MC&S (blood cultures and suspected site of infection)	Important for establishing evidence of infection and for targeting appropriate therapy but limited to manual audit and >50% negative.[9]	✓
No allergy or contra-indication to treatments	Important patient safety consideration but not relevant for resistance.	✗
Prompt administration of first dose	Important patient safety consideration in cases of severe sepsis but of uncertain relevance to resistance. Captured by sepsis CQUIN audits.	✗

Treatment regimen adequate to cover most likely pathogens	Meta-analysis of RCTs reports increased risk of mortality if initial regimen inadequate.[21] Relevance to resistance uncertain.	✓✉
Treatment regimen not unnecessarily broad spectrum	Indiscriminate use of critical broad-spectrum agents unnecessarily selects for resistance.[22-24]	✓✉
No redundant agents in treatment regimen	Unnecessary antibiotic exposure selects for avoidable resistance.[18-20]	✓
Treatment regimen compliant with local/national guideline or justified deviation	Validity dependent upon quality of local guideline. Relevance to resistance uncertain.	×
Treatment regimen cost-effective	Not relevant to resistance.	×
No underdosing	Limited evidence from modeling suggests that low doses may select resistance in pneumococci[25] but underdosing unlikely to be a problem in NHS hospitals due to pharmacist and nurse intervention.	×
No overdosing	Important patient safety consideration but likely to reduce rather than increase risk of selecting resistance.[26-31]	×
Correct route of administration	Relevant for efficacy, length of stay and risk of line infection but of uncertain relevance to resistance.	×
Prompt appropriate source control	Subjective assessment. Of uncertain relevance to resistance.	×

No missed doses or delayed doses	Of uncertain relevance to selection of resistance.	✖
Therapeutic drug monitoring (TDM) for narrow therapeutic index drugs	Important primarily for patient safety (but also for efficacy); of uncertain relevance to resistance.	✖
THEN FOCUS		
Prompt discontinuation of antibiotics if alternative diagnosis established and infection excluded	There is RCT evidence that unnecessary continuation selects for multi-resistant organisms.[32]	✓
Appropriate broadening of spectrum in response to MC&S results	This may necessitate an increase in broad-spectrum agent use if indicated by MC&S results. Failure to adjust ineffective treatment to MC&S results is associated with a higher risk of mortality.[33]	✓✉
Appropriate narrowing of spectrum in response to MC&S results	Evidence largely from observational studies suggests that de-escalation to narrow-spectrum agents is safe when patients are improving clinically and a plausible pathogen has been identified.[34]	✓✉
Prompt referral to OPAT services for suitable patients	Relevant for length of stay and risk of HCAI but of uncertain relevance to resistance.	✖
Prompt switch from IV to oral route of administration when safe and effective	Relevant for length of stay and risk of line infection but of uncertain relevance to resistance.	✖

Antibiotic plan documented in the notes	Good practice for continuity of care but of uncertain relevance to resistance.	×
No unjustified prolonged duration of treatment	There is evidence from RCTs and observational studies that unnecessarily prolonged duration selects for multi-resistant organisms.[32,35,36] Can only be audited at the end of therapy.	✓

*Prescribing elements relating to antibiotic spectrum; removed for pilot study

Selecting prescribing standards for audit

To reduce complexity for the purposes of a pilot evaluation of an appropriateness audit tool, the decision was taken to remove prescribing standards related to antibiotic spectrum (indicated by an asterisk in Table 1). A second component of this audit tool may subsequently be introduced to specifically address the evaluation of appropriateness antibiotic spectrum.

What are other countries doing?

The ECDC point prevalence survey (PPS) of HCAI and antimicrobial use has been criticised for failing to collect qualitative information about the appropriateness of the prescription.37 The PPS does not capture information on the justification for starting or continuing an antibiotic for community-acquired infections and cannot provide accurate course length data due to auditing many patients mid-treatment.

Infection specialists in Australia have adapted the ECDC point prevalence survey tool to better measure prescribing quality and this tool has performed well in validation, inter-rater reliability and user feedback.38 The Centers for Disease Control in Atlanta in the US have also published an audit

tool to evaluate the quality of inpatient antibiotic prescribing (http://www.cdc.gov/getsmart/healthcare/implementation.html .2

However, both the Australian and CDC tools have scope for refinement including assessment of evidence of infection, differentiating between evaluation of empirical or definitive pathogen-directed therapy and capturing justification for broad-spectrum prescribing. The existing tools also do not collect information on the potentially non-essential or avoidable days of antibiotic therapy and therefore cannot inform a goal for safe reduction of antibiotic consumption.

NEWS and qSOFA scores

In cases of undifferentiated sepsis, where signs or symptoms of infection do not appear to be localised to a discrete anatomical site, two patient acuity scoring systems have been incorporated into this draft audit tool to support the auditor in their assessment of evidence of infection and justification of antibiotic prescribing.

The National Early Warning Score (NEWS) was developed by the Royal College of Physicians and partners with the aim of standardising the assessment of acute-illness severity in the NHS.39 A 2015 study of 15 Welsh hospitals reported that 26% (290/1111) of adult inpatients with a NEWS ≥3 had sepsis (including severe sepsis) defined as high clinical suspicion of infection with systemic inflammatory response syndrome (SIRS≥2).40 This study, from Szakmany and colleagues, reported a median NEWS of 4 for patients meeting sepsis criteria compared with 5 for those meeting severe sepsis criteria.

Keep JW et al 2016 performed a retrospective study over one week in July 2013 of adult patients presenting to the ED of King's College Hospital, London, excluding patients with trauma.41 Of 500 patients included, 101/500 (20%) were 'patients with infection', 50/101 (49.5%) were reported as 'septic' (SIRS≥2), and 27/50 (54%) had severe sepsis (according to Surviving Sepsis Campaign definition 2012), representing 10% of patients and 5.4% of included patients respectively. The study identified 134/500 patients (27%) with NEWS ≥3 and of these 25/134 (18.6%) had severe sepsis. Applying NEWS ≥3 as a screening threshold for severe sepsis had a sensitivity of 92.6%, specificity of 77%, PPV of 18.7% and NPV of 99.5%. Two of 27 patients with severe sepsis had a NEWS of 2, representing a false negative rate in the target population of 7.5% for NEWS ≥3. Increasing the threshold to NEWS ≥4 resulted in an unacceptable false negative rate of 26% (7/27) of patients with severe sepsis.

Corfield AR et al 2014 screened 27,046 adult patients admitted to 20 Scottish hospitals for at least 2 days in 2009 for sepsis criteria using the Surviving Sepsis Campaign definition of 2012 and identified 5285 (19.5%) with SIRS≥2 (excluding patients with obvious non-infective pathology).42 9.7% of patients with sepsis had NEWS <3. Patients with sepsis had a median NEWS score of 7 and patients admitted to ICU had a significantly higher median NEWS score of 9 compared with non-ICU patients (median score 6). A single NEWS score of 7 or above in the ED for patients with sepsis was associated with a 27% chance of requiring ICU admission within 48 hours or 30-day mortality.

In summary, if a threshold of a NEWS score of 3 or above is applied for starting antibiotics, then it is anticipated that 7.5% of adult ED patients with severe sepsis will be denied antibiotics (Keep JW 2016) and 9.7% of adult ED patient with sepsis will be denied antibiotics (Corfield AR 2016). It therefore seems reasonable to assess what proportion of patients treated with antibiotics either have NEWS ≥3 or localised evidence of infection at an anatomical site. A prospective study to evaluate the use of NEWS to trigger antibiotic treatment has not been carried out so NEWS can only be used as a guide to the presence of a systemic inflammatory response.

The quick sequential organ failure assessment (qSOFA) score was proposed to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) as providing superior prediction of in-hospital mortality among adult patients with suspected infection outside of the ICU.43 The predictive validity for in-hospital mortality of qSOFA was assessed in almost 75,000 adult patients hospitalised with suspected infection and found to be statistically greater than SOFA and SIRS, supporting its use as a prompt to consider possible sepsis.44 A qSOFA score of 2 or more is proposed as the cut-off for sepsis (score one each for: RR >21; systolic BP 100 or lower; altered mental status).

A recent French study from Freund Y et al in 27 EDs (plus one each in Spain, Switzerland and Belgium) recruited consecutive patients presenting to ED with clinical suspicion of infection.45 Evidence of infection was confirmed retrospectively by 2 experts and patients with

localised infection and normal vital signs were excluded. Of the 879 patients included, 661 (75%) had qSOFA <2 and 22 (3.3%) of this cohort died (NPV 96.7%). 218 (25%) had qSOFA of 2 or more and 52 (24%) died. In contrast, 75% had SIRS of 2 or more. The AUROC was found to be significantly better for qSOFA (0.8) vs SIRS (0.65) to predict mortality, with similar results for predicting ICU admission.

Churpek MM et al 2017 screened adult admissions to a 500-bed university hospital in Chicago over an 8-year period and compared the performance of SIRS, qSOFA, MEWS and NEWS for predicting in-hospital mortality or ICU admission.46 The final study cohort consisted of 30,677 patients who met the definition of suspicion of infection outside the ICU (ED or wards), with both antibiotics and cultures within a predefined time window. In-hospital mortality was 5% for the cohort and 24% were admitted to ICU. A NEWS score of 3 or above (87% of patients) had high sensitivity and identified 96.5% of patients who died; specificity was low at 6.2% and PPV was 5.5% (Appendix Table 1) so 94.5% of patients with a NEWS of 3 or more survived. The NPV of NEWS ≥3 was 96.9% in this cohort. A qSOFA score of 2 or above (38% of patients) had lower sensitivity and only identified 68.7% of patients who died; specificity was also low at 12.3% and PPV was 9.7% (Appendix Table 1) so 90.3% of patients with a qSOFA of 2 or more survived. NPV of qSOFA ≥2 was 97.3% in this cohort. The AUROC was found to be significantly better for NEWS (0.77) vs qSOFA (0.69) to predict mortality.

In summary, applying qSOFA score ≥2 during ED or ward stay as a prediction tool for in-hospital all-cause mortality had a negative predictive value of 97% in adult patients with clinical suspicion of infection. A qSOFA score at a threshold of 2 or more, may be considered by some clinicians to be a reasonable tool for differentiating patients in whom immediate broad-spectrum antibiotics are justified, given the associated in-hospital mortality of 24% reported in the Freund ED study in France. However, as with NEWS, qSOFA has not been tested in a prospective study where it is used to dictate antibiotic treatment. The qSOFA is not an alert that alone will differentiate patients with infection from those without infection.

Limitations of the proposed audit

- The draft audit tool is intended to be used for adult patients in the first instance (qSOFA and NEWS not validated predictors of sepsis mortality in children).
- The draft audit tool considers antibiotics used for treatment of infection and is not designed for auditing peri-operative surgical prophylaxis.
- The audit must be carried out at the end of a course of treatment (or when a prescription stop date has been documented) in order to evaluate course length and this presents challenges with identifying patients prior to hospital discharge.
- Assessment of appropriateness is left to the discretion of the auditor and it is strongly recommended that the audit is undertaken by a health professional with expertise in infection. The assessment process should be aided by the available evidence of infection or sepsis, including qSOFA score, NEWS, CRP and white blood cell count. However, the decision remains a subjective one and the validity of this audit relies on the integrity of the auditor.

Validation of the proposed audit tool

The propsed audit tool will be subject to assessment of face-validity with a panel of UK infection specialists and in-use validation by comparing the appropriateness assessments of pairs of infection specialists (e.g. pharmacists and microbiologists or infectious diseases physicians).

1. Cusini A, Rampini SK, Bansal V, et al. Different patterns of inappropriate antimicrobial use in surgical and medical units at a tertiary care hospital in Switzerland: a prevalence survey. PLoS. One 2010;5(11):e14011.
2. Spivak ES, Cosgrove SE, Srinivasan A. Measuring Appropriate Antimicrobial Use: Attempts at Opening the Black Box. Clin Infect Dis 2016;63(12):1639-44.
3. Akhloufi H, Streefkerk RH, Melles DC, et al. Point prevalence of appropriate antimicrobial therapy in a Dutch university hospital. Eur. J. Clin. Microbiol. Infect. Dis 2015;34(8):1631-37.
4. Hecker MT, Aron DC, Patel NP, et al. Unnecessary use of antimicrobials in hospitalized patients: current patterns of misuse with an emphasis on the antianaerobic spectrum of activity. Arch. Intern. Med 2003;163(8):972-78.
5. Kumarasamy Y, Cadwgan T, Gillanders IA, et al. Optimizing antibiotic therapy-the Aberdeen experience. Clin. Microbiol. Infect 2003;9(5):406-11.
6. Lesprit P, de PA, Esposito-Farese M, et al. Postprescription review improves in-hospital antibiotic use: a multicenter randomized controlled trial. Clin. Microbiol. Infect 2015;21(2):180-87.
7. Roberts E, Dawoud DM, Hughes DA, et al. Evaluation of a consultant audit and feedback programme to improve the quality of antimicrobial prescribing in acute medical admissions. Int J Pharm Pract 2015;23(5):333-9.
8. Vlahovic-Palcevski V, Francetic I, Palcevski G, et al. Antimicrobial use at a university hospital: appropriate or misused? A qualitative study. Int J. Clin. Pharmacol. Ther 2007;45(3):169-74.
9. Braykov NP, Morgan DJ, Schweizer ML, et al. Assessment of empirical antibiotic therapy optimisation in six hospitals: an observational cohort study. Lancet Infect. Dis 2014;14(12):1220-27.
10. Mol PG, Gans RO, Panday PV, et al. Reliability of assessment of adherence to an antimicrobial treatment guideline. J. Hosp. Infect 2005;60(4):321-28.
11. Casaroto E, Marra AR, Camargo TZ, et al. Agreement on the prescription of antimicrobial drugs. BMC Infect Dis 2015;15:248.
12. Gyssens IC. Quality measures of antimicrobial drug use. Int. J. Antimicrob. Agents 2001;17(1):9-19.
13. Kunin CM, Tupasi T, Craig WA. Use of antibiotics. A brief exposition of the problem and some tentative solutions. Ann. Intern. Med 1973;79(4):555-60.
14. Willemsen I, Groenhuijzen A, Bogaers D, et al. Appropriateness of antimicrobial therapy measured by repeated prevalence surveys. Antimicrob. Agents Chemother 2007;51(3):864-67.
15. Ashiru-Oredope D, Sharland M, Charani E, et al. Improving the quality of antibiotic prescribing in the NHS by developing a new Antimicrobial Stewardship Programme: Start Smart--Then Focus. J. Antimicrob. Chemother 2012;67 Suppl 1:i51-i63.

16. Public_Health_England. Antimicrobial Stewardship: "Start Smart - Then Focus". Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI) 2015. https://www.gov.uk/government/publications/antimicrobial-stewardship-start-smart-then-focus.
17. van den Bosch CM, Geerlings SE, Natsch S, et al. Quality indicators to measure appropriate antibiotic use in hospitalized adults. Clin Infect Dis 2015;60(2):281-91.
18. Lopez-Lozano JM, Monnet DL, Yague A, et al. Modelling and forecasting antimicrobial resistance and its dynamic relationship to antimicrobial use: a time series analysis. Int. J. Antimicrob. Agents 2000;14(1):21-31.
19. Tacconelli E, Cataldo MA, De PG, et al. Prediction models to identify hospitalized patients at risk of being colonized or infected with multidrug-resistant Acinetobacter baumannii calcoaceticus complex. J. Antimicrob. Chemother 2008;62(5):1130-37.
20. Tacconelli E, De AG, Cataldo MA, et al. Antibiotic usage and risk of colonization and infection with antibiotic-resistant bacteria: a hospital population-based study. Antimicrob. Agents Chemother 2009;53(10):4264-69.
21. Paul M, Shani V, Muchtar E, et al. Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. Antimicrob. Agents Chemother 2010;54(11):4851-63.
22. Harris AD, Perencevich E, Roghmann MC, et al. Risk factors for piperacillin-tazobactam-resistant Pseudomonas aeruginosa among hospitalized patients. Antimicrob. Agents Chemother 2002;46(3):854-58.
23. Lai CC, Wang CY, Chu CC, et al. Correlation between antibiotic consumption and resistance of Gram-negative bacteria causing healthcare-associated infections at a university hospital in Taiwan from 2000 to 2009. J. Antimicrob. Chemother 2011;66(6):1374-82.
24. Pakyz AL, Oinonen M, Polk RE. Relationship of carbapenem restriction in 22 university teaching hospitals to carbapenem use and carbapenem-resistant Pseudomonas aeruginosa. Antimicrob. Agents Chemother 2009;53(5):1983-86.
25. Opatowski L, Mandel J, Varon E, et al. Antibiotic dose impact on resistance selection in the community: a mathematical model of beta-lactams and Streptococcus pneumoniae dynamics. Antimicrob. Agents Chemother 2010;54(6):2330-37.
26. Guillemot D, Carbon C, Balkau B, et al. Low dosage and long treatment duration of beta-lactam: risk factors for carriage of penicillin-resistant Streptococcus pneumoniae. JAMA 1998;279(5):365-70.
27. Handel A, Margolis E, Levin BR. Exploring the role of the immune response in preventing antibiotic resistance. J. Theor. Biol 2009;256(4):655-62.
28. Martinez MN, Papich MG, Drusano GL. Dosing regimen matters: the importance of early intervention and rapid attainment of the pharmacokinetic/pharmacodynamic target. Antimicrob. Agents Chemother 2012;56(6):2795-805.
29. Olofsson SK, Cars O. Optimizing drug exposure to minimize selection of antibiotic resistance. Clin. Infect. Dis 2007;45 Suppl 2:S129-S36.
30. Schrag SJ, Pena C, Fernandez J, et al. Effect of short-course, high-dose amoxicillin therapy on resistant pneumococcal carriage: a randomized trial. JAMA 2001;286(1):49-56.

31. Tam VH, Louie A, Deziel MR, et al. The relationship between quinolone exposures and resistance amplification is characterized by an inverted U: a new paradigm for optimizing pharmacodynamics to counterselect resistance. Antimicrob. Agents Chemother 2007;51(2):744-47.
32. Singh N, Rogers P, Atwood CW, et al. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. Am. J. Respir. Crit Care Med 2000;162(2 Pt 1):505-11.
33. Palacios-Baena ZR, Gutierrez-Gutierrez B, De Cueto M, et al. Development and validation of the INCREMENT-ESBL predictive score for mortality in patients with bloodstream infections due
to extended-spectrum-beta-lactamase-producing Enterobacteriaceae. J Antimicrob Chemother 2017;72(3):906-13.
34. Schuts EC, Hulscher ME, Mouton JW, et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. Lancet Infect. Dis 2016;16(7):847-56.
35. Chastre J, Wolff M, Fagon JY, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA 2003;290(19):2588-98.
36. Marra AR, de Almeida SM, Correa L, et al. The effect of limiting antimicrobial therapy duration on antimicrobial resistance in the critical care setting. Am J Infect Control 2009;37(3):204-9.
37. Kieran JA, O'Doherty RG, Hudson BJ. ESAC point prevalence methodology to assess antimicrobial consumption and quality of prescribing in an Australian setting. Med. J. Aust 2011;194(2):103-04.
38. James R, Upjohn L, Cotta M, et al. Measuring antimicrobial prescribing quality in Australian hospitals: development and evaluation of a national antimicrobial prescribing survey tool. J. Antimicrob. Chemother 2015;70(6):1912-18.
39. Physicians RCo. National Early Warning Score (NEWS): Standardising the assessment of acute illness severity in the NHS. Report of a working party. https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news, 2012.
40. Szakmany T, Lundin RM, Sharif B, et al. Sepsis Prevalence and Outcome on the General Wards and Emergency Departments in Wales: Results of a Multi-Centre, Observational, Point Prevalence Study. PLoS One 2016;11(12):e0167230.
41. Keep JW, Messmer AS, Sladden R, et al. National early warning score at Emergency Department triage may allow earlier identification of patients with severe sepsis and septic shock: a retrospective observational study. Emerg Med J 2016;33(1):37-41.
42. Corfield AR, Lees F, Zealley I, et al. Utility of a single early warning score in patients with sepsis in the emergency department. Emerg Med J 2014;31(6):482-7.
43. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315(8):801-10.
44. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315(8):762-74.

45. Freund Y, Lemachatti N, Krastinova E, et al. Prognostic Accuracy of Sepsis-3 Criteria for In-Hospital Mortality Among Patients With Suspected Infection Presenting to the Emergency Department. JAMA 2017;317(3):301-08.
46. Churpek MM, Snyder A, Han X, et al. Quick Sepsis-related Organ Failure Assessment, Systemic Inflammatory Response Syndrome, and Early Warning Scores for Detecting Clinical Deterioration in Infected Patients outside the Intensive Care Unit. Am J Respir Crit Care Med 2017;195(7):906-11.