Antimicrobial stewardship: prescribing antibiotics

Key therapeutic topic
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Options for local implementation

- Antibiotic resistance poses a significant threat to public health, especially because antibiotics underpin routine medical practice.

- Review and, if appropriate, revise prescribing and local policies that relate to antimicrobial stewardship to ensure these are in line with the NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use. A NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population is in development (publication expected January 2017).

- Review and, if appropriate, optimise current prescribing practice and use implementation techniques to ensure prescribing is in line with Public Health England (PHE) guidance on managing common infections, the Department of Health’s guidance Start smart – then focus, local trust antimicrobial guidelines and the Antimicrobial Stewardship in Primary Care collaboration TARGET antibiotics toolkit.

- Review the following against local and national prescribing criteria:
  - total volume of antibiotic prescribing
  - prescribing of quinolones, cephalosporins, co-amoxiclav and other broad-spectrum antibiotics
  - prescribing of 3-day courses of trimethoprim, nitrofurantoin and pivmecillinam.
Evidence context

Antimicrobial resistance and stewardship

Antimicrobial resistance poses a significant threat to public health, especially because antibiotics underpin routine medical practice. The Chief Medical Officer's report on the threat of antimicrobial resistance and infectious diseases (2013) highlights that, while a new infectious disease has been discovered nearly every year for the past 30 years, there have been very few new antibiotics developed. This is leaving the armoury nearly empty as diseases evolve and become resistant to existing drugs. The report highlights that looking after the current supply of antibiotics is equally as important as encouraging development of new drugs.

According to the English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report (2015), the rates of Escherichia coli and Klebsiella pneumoniae bloodstream infections increased by 15.6% and 20.8% respectively from 2010 to 2014 (with associated increases in the numbers of people with antibiotic resistant infections) and further increases of 4.6% and 9% respectively were seen from 2014 to 2015 (ESPAUR report 2016). Nevertheless, for other bacteria where there have been targeted interventions to reduce the burden of infection or resistance, infection rates or proportions of infections where resistance is detected have declined. For example, according to the 2015 report, meticillin-resistant Staphylococcus aureus (MRSA) bloodstream infections have reduced from 12% to 8% over the last 5 years through effective infection prevention and control within healthcare settings.

As stated by the ESPAUR report (2015), good antimicrobial stewardship is a cornerstone for both effective treatment of infections and reduction of antimicrobial resistance. Antimicrobial stewardship programmes contain analysis of local antimicrobial resistance data to guide the development of evidence-based prescribing guidelines, educational resources to improve clinical practices to ensure antibiotics are prescribed appropriately, restrictive and persuasive interventions to use the appropriate antibiotics, and audit and feedback to clinical staff to improve patient care and outcomes against local and national prescribing criteria designed to drive quality improvements.

NICE has published a guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use and a guideline on antimicrobial stewardship: changing risk-related behaviours in the general population is in development (publication expected January 2017). Public Health England (PHE) has published an antimicrobial resistance resource handbook, which collates national resources on antimicrobial resistance, antimicrobial stewardship and infection prevention and control. NHS England has also collated information on addressing antimicrobial resistance.
Resources include 2 national toolkits to support implementation of antimicrobial stewardship best practice: Treat antibiotics responsibly, guidance, education, tools (TARGET) for primary care and ‘Start smart, then focus’ for secondary care. A dental antimicrobial stewardship toolkit is also available.

The ESPAUR report (2015) states that, in 2014, 60% of clinical commissioning groups (CCGs) and 87% of NHS acute trusts had reviewed the national antimicrobial stewardship toolkits for primary or secondary care; however, only 13% of CCGs and 46% of acute trusts had implemented an action plan to deliver antimicrobial stewardship activities. The ESPAUR report (2016) found that antimicrobial stewardship continued to improve in general practice and hospitals, but further work is needed in community health trusts.

**Antibiotic prescribing**

To help prevent the development of resistance it is important to only prescribe antibiotics when they are necessary, and not for self-limiting mild infections such as colds and most coughs, sinusitis, earache and sore throats. PHE guidance on managing common infections in primary care recommends that consideration should be given to a no, or back-up or delayed antibiotic strategy for acute self-limiting upper respiratory tract infections and mild urinary tract infections (UTIs). It also advises that people are given supporting information about antibiotic strategies, infection severity and usual duration.

The PHE guidance recommends that simple generic antibiotics should be used if possible when antibiotics are necessary. Broad-spectrum antibiotics (for example, co-amoxiclav, quinolones and cephalosporins) need to be reserved to treat resistant disease. They should generally be used only when narrow-spectrum antibiotics are ineffective because they increase the risk of MRSA, *Clostridium difficile* and resistant UTIs.

Addressing healthcare-associated *Clostridium difficile* infection remains a key issue on which NHS organisations have been mandated to implement national guidance. The Department of Health and Public Health England’s report on *Clostridium difficile* infection: how to deal with the problem from 2008 recommends that trusts should develop restrictive antibiotic guidelines that use narrow-spectrum agents alone or in combination as appropriate. The report suggests that these guidelines should avoid recommending clindamycin and second- and third-generation cephalosporins (especially in older people) and should recommend minimising the use of quinolones, carbapenems (for example, imipenem and meropenem) and prolonged courses of aminopenicillins (for example, ampicillin and amoxicillin). Broad-spectrum antibiotics should be used only when indicated by the
person’s clinical condition, and their use should be reviewed after the results of microbiological testing or based on the sensitivities of causative bacteria.

The Department of Health Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI) recommends the Start smart – then focus approach. This advises that, if immediate antibiotic treatment is necessary, the clinical diagnosis and continuing need for antibiotics should be reviewed within 48–72 hours. A study of Start smart – then focus, which was discussed in a NICE eyes on evidence article on implementation of antibiotic prescribing guidance, concluded that most hospital antibiotic policies in England 'start smart' by recommending broad-spectrum antibiotics for empirical therapy in severe infections. However fewer ‘focus’ by reviewing the ongoing need for antibiotics after a couple of days, as recommended.

A NICE evidence summary: medicines and prescribing briefing on Clostridium difficile infection: risk with broad-spectrum antibiotics outlines 3 meta-analyses on this infection. The first of these, Slimings and Riley (2014), concluded that cephalosporins and clindamycin are the antibiotics most strongly associated with hospital-associated C. difficile infection. Subgroup analyses showed that, although first-generation cephalosporins appear to carry a lower risk of C. difficile infection than second- or third-generation cephalosporins, there is no definitive evidence to prove this. Also, co-amoxiclav and piperacillin-tazobactam were associated with an increase in the risk of infection. The other 2 meta-analyses, Brown et al. (2013) and Deshpande et al. (2013), found that, for community-associated infection, the strongest association was seen with clindamycin, cephalosporins and quinolones. Trimethoprim and sulfonamides (co-trimoxazole) were associated with an increased risk of infection in all 3 meta-analyses but data were not reported for trimethoprim alone, which is most commonly used in England. The 3 meta-analyses have many limitations and, because of those limitations and the observational nature of the studies, they cannot definitively establish a causal relationship between particular antibiotics and C. difficile infection. Changes in antibiotic prescribing practice, the frequent use of multiple antibiotics and other potential confounding factors make it difficult to determine the relative risk for individual antibiotics.

The C. difficile ribotyping network (CDRN) report (2013–2015), published by Public Health England, found that the strains of C. difficile identified and the antibiotics most frequently reported as being associated with C. difficile infections referred to the CDRN have changed markedly. In 2007/08, cephalosporins and quinolones were the most commonly cited antibiotics, but have since been superseded by co-amoxiclav and piperacillin-tazobactam. The report states that these data are likely to reflect real changes in prescribing of systemic antibiotics as one of the control measures for C. difficile infection.
These data should be interpreted with caution and should not be considered to indicate conclusively which antibiotics have the highest risks of *C. difficile* infection. Nevertheless, they show that antibiotic prescribing practice and the epidemiology of *C. difficile* infections are changing. The NICE evidence summary concludes that, without clear evidence showing that 1 particular antibiotic or class of antibiotic is ‘low-risk’, only general recommendations are possible and healthcare professionals should follow antibiotic guidelines that recommend that all broad-spectrum antibiotics are prescribed appropriately and with careful stewardship.

The ESPAUR report (2015) showed that, in general practice, use of quinolones decreased and use of cephalosporins and carbapenems remained unchanged, but use of penicillins plus an enzyme inhibitor (such as co-amoxiclav or piperacillin-tazobactam) increased between 2010 and 2014. In hospitals, the use of quinolones remained unchanged and use of penicillins plus an enzyme inhibitor, cephalosporins and carbapenems increased during the same period. The ESPAUR report (2016) found that broad-spectrum antibiotic use continued to decrease in primary care, and England now uses the lowest amounts of cephalosporins and quinolones in the EU. However, despite low levels of use of cephalosporins and resistance, the proportion of bloodstream infections resistant to these antibiotics has not changed significantly in the last 5 years. Also, hospitals continue to increase their antibiotics of last resort currently available: piperacillin/tazobactam, carbapenems and colistin.

According to PHE guidance on managing common infections, cefalexin and other cephalosporins (cefixime, cefotaxime and ceftriaxone) should be used only in limited situations (for example, second-line in upper and lower UTI in children, and third-line in UTI in women who are pregnant). Clindamycin is recommended only for bacterial vaginosis (as a vaginal cream) and unresolving cellulitis, and is an option for dental abscess in limited circumstances.

The prescribing of quinolones (for example, ciprofloxacin and ofloxacin) in general practice is also a cause for concern. Resistance to quinolones has increased at a considerable rate (for example, quinolone-resistant *Neisseria gonorrhoeae*) and is usually high level, affecting all the quinolones (see Susceptibility testing of *N. gonorrhoeae* for details). PHE guidance on managing common infections recommends that quinolones are used as first-line treatment only for acute pyelonephritis, acute prostatitis, epididymitis and pelvic inflammatory disease. It states that they should be used in lower respiratory tract infections only when there is proven resistance to other antibiotics.

Although identifying the cephalosporin and quinolone classes as 'high-risk' may have been an important control measure in reducing the risk of *C. difficile* infection, an unintended consequence of this may have been a recent increase in clinically inappropriate prescribing of co-amoxiclav and other broad-spectrum antibiotics, such as piperacillin-tazobactam. These antibiotics have a very
limited set of recommended clinical indications. According to the PHE guidance, in primary care, co-amoxiclav is recommended only for persistent acute rhinosinusitis, upper UTI in children, acute pyelonephritis, facial cellulitis, and the prophylaxis and treatment of infection after bites. It may be used second-line in acute exacerbations of chronic obstructive pulmonary disease if infection is resistant to first-line options, and as an option for dental abscess in limited circumstances. Piperacillin-tazobactam is an intravenous antibiotic and is not generally used in primary care.

According to the [ESPAUR report (2015)](https://www.espaur.com/), with the reductions in cephalosporin and quinolone use in England in the last decade, co-amoxiclav and piperacillin-tazobactam have become key agents in many hospital empiric antibiotic policies. They have a key role in treating hospital sepsis syndromes, particularly those related to intra-abdominal sepsis or sepsis without a defined source. The use of carbapenems is also almost exclusively within hospitals for suspected or confirmed multi-drug resistant Gram-negative infections, usually in intensive care, transplant or cancer units. Between 2013 and 2014, prescription of carbapenems and piperacillin-tazobactam rose by 4% and 7% respectively, with total increases between 2010 and 2014 of 36% and 55% respectively.

The [ESPAUR report (2016)](https://www.espaur.com/) states that the proportions of bloodstream infections that were resistant to piperacillin-tazobactam rose dramatically between 2011 and 2015 (from 8.5% to 11.7% for those caused by *E. coli* and from 12.6% to 18.5% for those caused by *K. pneumoniae*). The report notes that these increases in resistance will increase the pressure on clinicians to use carbapenems (which are the antibiotics of last resort) unless alternative treatment strategies are developed. Although carbapenem resistance remains low in bloodstream infections in England (*E. coli* 0.2% and *K. pneumoniae* 1.1%), there have been year-on-year increases in the numbers of bacteria confirmed to produce carbapenemases (enzymes that break down carbapenems making them ineffective for treatment). The 2016 report advises that, based on resistance data, combinations of antibiotics (such as co-amoxiclav plus amikacin) are possible alternatives to single antibiotics for empiric therapy of sepsis, preserving carbapenems and putting less selection pressure on antibiotics such as piperacillin-tazobactam.

Co-trimoxazole is not recommended in PHE guidance for primary care for any infections. However, the [ESPAUR report (2015)](https://www.espaur.com/) states that use increased by 5% between 2011 and 2014. The [British National Formulary](https://www.cmhl.nhs.uk/bnf) advises that co-trimoxazole is associated with rare but serious side effects (for example, Stevens-Johnson syndrome, bone marrow depression and agranulocytosis) and states that it should only be considered for UTI and acute exacerbations of chronic bronchitis when there is bacteriological evidence of sensitivity to co-trimoxazole and good reason to prefer this combination to a single antibacterial; similarly it should only be used in acute otitis media in children when there is good reason to prefer it.
Three-day courses of antibiotics for uncomplicated urinary tract infection

According to PHE guidance, a 3-day course of antibiotics is sufficient for acute symptomatic UTI in most women with no fever or flank pain who are not pregnant. Nitrofurantoin is recommended first-line for people with a glomerular filtration rate (GFR) of over 45 ml/min because general resistance and community multi-resistant *E. coli* are increasing. If GFR is between 30 and 45 ml/min, nitrofurantoin should be used only if drug resistance is a problem and there is no alternative (see the September 2014 edition of Drug Safety Update for more information). Depending on local resistance patterns, or if GFR is less than 45 ml/min, trimethoprim or pivmecillinam are recommended as alternative first-line options. PHE recommends that risk factors for resistance should be considered and culture and sensitivity testing should be performed if first-line treatment for UTI fails. PHE has produced guidance for primary care on diagnosing UTI and understanding culture results.

The ESPAUR report (2016) found that there is wide variation in the rates of resistance to trimethoprim (and other antibiotics) across England. In Gram-negative UTI, trimethoprim resistance ranges from 16.3% to 66.7% across CCGs. This may be related to variation in sending urine samples for laboratory testing. However, the report states that 86% of CCGs have resistance rates greater than 25%, highlighting that trimethoprim can no longer be advised as the first-line empiric antibiotic treatment for UTIs in England.

More information on managing common infections can be found in the NICE clinical knowledge summaries, the NICE guidelines on respiratory tract infections and pneumonia and the NICE pathway on self-limiting respiratory tract infections – antibiotic prescribing. A NICE pathway on prevention and control of healthcare-associated infections brings information on this subject together. NICE is also developing a guideline on managing common infections.

NICE has published quality standards on infection prevention and control and surgical site infection, which are concise sets of prioritised statements designed to drive measurable quality improvements within these areas. PHE has also published surveillance of surgical site infections in NHS hospitals in England 2015/16, which aligns with these standards. The Department of Health webpage on antimicrobial resistance includes resources for healthcare professionals to help improve infection prevention and control practices and prescribing.

Prescribing data

In April 2016, NHS England launched a national programme to reduce inappropriate antibiotic prescribing. The payments form part of 2 schemes that reward excellence and quality improvement
in the NHS: the Commissioning for Quality and Innovation (CQUIN) and the Quality Premium scheme. CCG performance against the antimicrobial resistance quality premium is reported monthly via the NHS England Antibiotic quality premium monitoring dashboard. Data from May 2016 showed the total number of antibiotics prescribed by GPs was down by 7.3% in 1 year (a total of 2,696,143 fewer items) and the use of broad-spectrum antibiotics was reduced by 16% (a reduction of over 600,000 items).

For 2016/17, a new CCG improvement and assessment framework was also launched, which includes antimicrobial resistance indicators.

The Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI), which provides advice to the government on minimising the risk of healthcare associated infections, has agreed antimicrobial prescribing quality measures for primary and secondary care.

Three medicines optimisation key therapeutic topic (MO KTT) prescribing comparators are available to support this key therapeutic topic\(^1\). These are:

- **Antibacterial items/STAR-PU**: the number of prescription items for antibacterial drugs (BNF 5.1) per Oral antibacterials (BNF 5.1 sub-set) ITEM based Specific Therapeutic Group Age-sex weightings Related Prescribing Unit (STAR-PU).

- **Co-amoxiclav, cephalosporins & quinolones % items**: the number of prescription items for co-amoxiclav, cephalosporins and quinolones as a percentage of the total number of prescription items for selected antibacterial drugs (BNF 5.1 sub-set).

- **3 day courses of antibiotics: ADQ/item**: the number of average daily quantities (ADQs) per item for trimethoprim 200 mg tablets, nitrofurantoin 50 mg tablets and capsules, nitrofurantoin 100 mg m/r capsules and pivmecillinam 200 mg tablets.

**Antibacterial items/STAR-PU**

- Data for 2015/16 (April 2015 to March 2016) show a 2.32 fold variation in prescribing rates at Clinical Commissioning Group (CCG) level, from 0.62 to 1.44 items/STAR-PU.

- Between the 3-month period January to March 2014 and the 3-month period January to March 2016 there was a 5.7% decrease in the comparator value for England (total prescribing) from 0.314 to 0.296 items/STAR-PU.

- Over the same period there was an 8.18% increase in the variation between CCGs, as measured by the inter-decile range, an absolute increase of 0.007 items/STAR-PU. The inter-
decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.

**Co-amoxiclav, cephalosporins & quinolones % items**

- Data for 2015/16 (April 2015 to March 2016) show a 3.4 fold variation in prescribing rates at CCG level, from 4.07% to 14.02%.

- Between the 3-month period January to March 2014 and the 3-month period January to March 2016 there was a 19.9% decrease in the comparator value for England (total prescribing) from 10.6% to 8.5%.

- Over the same period there was a 32.9% decrease in the variation between CCGs, as measured by the inter-decile range, an absolute decrease of 2.41%. The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.

**3 day courses of antibiotics: ADQ/item**

- Data for the 3-month period July to September 2016 show a 1.6 fold variation in prescribing rates at CCG level, from 4.87 to 7.65 ADQ/item.

- Between the 3-month period October to December 2013 and the 3-month period July to September 2016 there was a 6.7% decrease in the comparator value for England (total prescribing) from 6.15 to 5.74 ADQ/item.

- Over the same period there was a 15.0% increase in the variation between CCGs, as measured by the inter-decile range, an absolute increase of 0.15 ADQ/item. The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.

The **Medicines optimisation dashboard**, which brings together a range of medicines-related metrics from across sectors, includes the first 2 prescribing comparators outlined above. The medicines optimisation dashboard helps NHS organisations to understand how well their local populations are being supported to optimise medicines use and inform local planning. The dashboard allows NHS organisations to highlight variation in local practice and provoke discussion on the appropriateness of local care. It is not intended as a performance measurement tool and there are no targets.
The comparator and associated data presented here are based on the previous Key therapeutic topics publication (February 2016). Data provided by NHS Digital (October 2016; source: Information Services Portal, Business Services Authority). For details of any update to the comparators refer to the NHS Digital website and the Information Services Portal, Business Services Authority.

Update information

January 2017: This topic was retained for the 2017 update of medicines optimisation: key therapeutic topics. The focus has been changed to antimicrobial stewardship, and this topic now also includes key information from the 3-day courses of antibiotics for uncomplicated urinary tract infection topic. The evidence context has been updated in the light of new guidance and important new evidence.

About this key therapeutic topic

This document summarises the evidence base on this key therapeutic topic which has been identified to support medicines optimisation. It is not formal NICE guidance.

For information about the process used to develop the Key therapeutic topics, see the integrated process statement.

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