Medicines Evidence Commentary

Antimicrobial stewardship: reducing the incidence of colonisation with antibiotic-resistant bacteria and Clostridium difficile infection

The authors of a meta-analysis of 32 studies found that antimicrobial stewardship (AMS) programmes reduced the incidence of infection and colonisation with multi-drug resistant Gram-negative bacteria, methicillin-resistant Staphylococcus aureus (MRSA) and Clostridium difficile in hospital inpatients. This reduction was significantly marked when combined with infection control measures, particularly hand hygiene. Health and social care practitioners, commissioners and providers should follow the NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use.

Overview and current advice

In 2016, an independent review commissioned by the UK Government to explore the growing threat of antimicrobial resistance (AMR) estimated that by 2050, unless action is taken, 10 million lives a year will be at risk because of the rise of drug-resistant infections worldwide. Moreover, if antimicrobials lose their effectiveness, key medical procedures (such as gut surgery, caesarean sections, joint replacements, and treatments that depress the immune system, such as chemotherapy for cancer) could become too dangerous to perform.

The UK 5-year AMR strategy (2013–2018) from the Department of Health aims to limit the development and spread of antimicrobial resistant organisms through a set of actions arising from 3 strategic aims:

- Improved understanding of AMR
- Development of new antibiotics and diagnostic tools
- Careful stewardship of existing treatments.

In its guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use, NICE defines antimicrobial stewardship (AMS) as an organisational or healthcare system-wide approach to promoting and monitoring the judicious use of antimicrobials in order to preserve their future effectiveness. Public Health England 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: the TARGET antibiotics toolkit for primary care and ‘Start smart, then focus’ for secondary care. A dental antimicrobial stewardship toolkit is also available.
The NICE Pathway: antimicrobial stewardship brings together all related NICE guidance and associated products on the condition in a set of interactive flow charts. NICE has also produced a Key Therapeutic Topic on antimicrobial stewardship: prescribing antibiotics.

New evidence

Authors of a systematic review and meta analysis of 32 studies have found that AMS programmes significantly reduced the incidence of infection and colonisation of antimicrobial-resistant bacteria and Clostridium difficile (C. difficile) infection in hospitalised patients (Baur et al 2017). The effectiveness of this intervention was increased in 10 (31%) studies, where AMS programmes were co-implemented with infection control measures, most frequently hand hygiene (8 [25%] studies).

The meta-analysis included 32 studies conducted between 1992 and 2014 in 20 countries, analysing a total of 9,056,241 patient-days. Countries most represented were the USA (5 studies), Japan (4 studies), Germany and France (3 studies each); 2 studies took place in the UK. The authors assessed these for quality using recognised standards; 2 were judged to be of high quality, 26 of moderate quality and 4 of low quality. The primary outcome was measured as the incidence ratio (IR), calculated as the ratio between the incidence of colonisation (the number of antibiotic-resistant bacteria isolated per 1000 patient-days) or infection with the targeted antibiotic-resistant bacteria or C. difficile infection before and after implementation of an antibiotic stewardship programme. Secondary outcomes were the IRs by study settings, type of antibiotic stewardship intervention, and concomitant implementation of infection control measures.

Several AMS interventions were investigated in the included studies with the most frequent intervention focusing on audit (19 [59%] studies) and the implementation of policies to restrict access to antimicrobials (15 [47%] studies). Investigators found that the most effective AMS intervention was antibiotic cycling which yielded the largest reduction in AMR (IR 0.49, 95% CI 0.34 to 0.72, p=0.003). However only 3 studies investigated this type of intervention, with 2 out of 3 exclusively investigating antibiotic cycling and 1 study investigating a combination of this intervention with antibiotic restriction and audit.

The authors found that implementation of AMS was associated with about a halving in incidence of multidrug-resistant Gram-negative bacteria (IR 0.49, 95% confidence interval [CI] 0.35 to 0.68, p<0.0001) and extended-spectrum beta-lactamase producing Gram-negative bacteria (IR 0.52, 95% CI 0.27 to 0.98, p=0.04). A reduction in the incidence of the multidrug-resistant Gram-negative bacteria was also seen in the subgroup of studies focusing on carbapenem resistance (IR 0.57, 95% CI 0.40 to 0.81; p=0.002). However, these reductions were not statistically significant when effects were stratified by specific Gram-negative organism. The incidence of aminoglycoside-resistant and quinolone-resistant Gram-negative bacteria was also not statistically significantly reduced.

Among the Gram-positive organisms investigated, the incidence of aminoglycoside-resistant, quinolone-resistant and vancomycin-resistant organisms was not significantly affected by AMS programmes. However, incidence of methicillin-resistant Staphylococcus aureus (MRSA) was reduced by more than a third (IR 0.63, 95% CI 0.45 to 0.88, p=0.007). Similarly, there was a 32% reduction (IR 0.68, 95% CI 0.53 to 0.88, p=0.003) in C. difficile infection.

The authors concluded that combining hand hygiene with AMS interventions reduced antimicrobial resistance substantially (IR 0.34, 95% CI 0.21 to 0.54; p<0.0001), whereas in studies of AMS without hand hygiene the reduction was smaller (IR 0.83, 95% CI 0.71 to 0.98, p=0.03).
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The results from this systematic review and meta-analysis support the work of AMS programmes in hospitals, in line with current practice and guidance and should provide encouragement to those working hard in this field. Of particular note are the reductions in infection with carbapenem-resistant Gram-positive bacteria (since carbapenems are antibiotics of last resort), MRSA and C. difficile. Furthermore, the results show the importance of combining infection control measures with AMS, especially hand hygiene, which serves as a useful reminder for healthcare leaders to promote good practice in the health system in this way.

Stratification relating to the type of intervention employed by AMS programmes may inform current guidance, which typically do not comment on which AMS intervention to use. Half of the studies investigated a combination of 2 or more interventions which is reflective of current clinical practice as a combination of efforts is typically used. Nevertheless, it is difficult to ascertain distinctions between the AMS interventions in the absence of investigating them exclusively.

Limitations to this systematic review and meta-analysis arise from the substantial variation between the studies included, with the heterogeneity assessment for bacterial species and resistance patterns producing extremely large values at 90.2% and 94.5% respectively. This suggests that there was significant variation between the species of bacteria investigated and resistance reported between studies.

Although the 11 studies investigating C. difficile infection produced results for the same organism, similar levels of variation were shown ($I^2 = 80.2\%$). This highlights the likelihood of other possible variations such as the study design and study setting. All studies were conducted in hospitals but some investigated the entire population of a hospital whereas others were confined to specific wards such as surgical intensive care units or older-people’s wards. Indeed, this conveys disparity in subject population since the age of patients is likely to differ greatly between wards. The English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report 2016 found that rates of Escherichia coli (E. coli) bacteraemia resistant to third-generation cephalosporins or ciprofloxacin in patients differed substantially with age.

Although there is variation within the data, the results point in the right direction by supporting the use of AMS programmes within hospitals. These results can be applied to a UK population since the organisms investigated are prevalent within the UK health system. As antibiotic prescribing mostly occurs outside of hospitals, research in other settings will also help to inform a wider picture of clinical practice.

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References

About this Medicines Evidence Commentary

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