Antibiotic prescribing: adverse events with antibiotic use in people who are hospitalised

A US retrospective cohort study found that approximately one-fifth of adult hospital in-patients who received an antibiotic experienced an adverse event. The risk of an adverse event increased with the duration of treatment. Some classes of antibiotic were more likely to be associated with an adverse event. Using local antimicrobial guidelines the investigators suggested that 19% of antibiotic regimens were not clinically indicated. These findings highlight the importance of prudent antibiotic use, as described in the NICE guideline on antimicrobial stewardship.

Overview and current advice

Antibiotic use in hospital is common, with around 1 in 3 people in hospitals in England on an antibiotic at any one time (Health matters: antimicrobial resistance, Public Health England, 2015). Overuse or inappropriate use of antibiotics allows bacteria to develop resistance. The 2016 English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report states that total antibiotic consumption in England fell by 4.3% between 2014 and 2015. The majority of antibiotic prescribing in England occurs in general practice (74%), followed by hospital inpatients (11%), outpatients (7%), dental practice (5%) and other community settings (3%).

The NICE guideline on antimicrobial stewardship covers the effective use of antimicrobials (including antibiotics), aiming to change prescribing practice to help slow the emergence of antimicrobial resistance and ensure that antimicrobials remain an effective treatment for infection. NICE is currently developing a new series of guidelines for managing common infections. This set of approximately 30 antimicrobial prescribing guidelines will help frontline healthcare workers in the battle against antimicrobial resistance (AMR) by preventing unnecessary use of these medicines. For more information see this NICE news article.

The Public Health England toolkit Antimicrobial stewardship: Start smart - then focus provides an outline of evidence-based antimicrobial stewardship in the secondary healthcare setting. The principles of ‘Start smart – then focus’ are to not start antibiotics in the absence of clinical evidence of bacterial infection, and review the clinical diagnosis and the continued need for antibiotics by 48 to 72 hours (note: due to advances in rapid diagnostics it may be possible to review prior to 48 hours after first dose).
New evidence

A US retrospective cohort study investigated the incidence of antibiotic-associated adverse events (AEs) in adults who were hospitalised and receiving systemic antibiotics (Tamma et al. 2017).

The investigators collected data on all people aged 18 years and over who were admitted to 4 general medicine wards at John Hopkins Hospital, Baltimore, Maryland, US between September 2013 and June 2014. All adults who received antibiotics for 24 hours or more were eligible for inclusion. People receiving antibiotic prophylaxis with no clear stop dates, antibiotics used for non-infective indications (for example, rifaximin for hepatic encephalopathy), topical or inhaled antibiotics or anti-tuberculosis regimens were excluded. Antibiotic prescribing was assessed for appropriateness using the John Hopkins Hospital Antibiotic Management Guidelines. Participants were examined for 30 days after starting treatment for antibiotic-associated AEs (gastrointestinal, dermatological, musculoskeletal, haematological, hepatobiliary, renal, cardiac, and neurological), and for 90 days for the development of Clostridium difficile infection or incident multidrug-resistant organism infection.

In total 5,579 people were admitted during the study period, of whom 1,488 (27%) received an antibiotic for at least 24 hours and were included in the analysis. The median age was 59 years, 51% of participants were female and the median hospital stay was 4 days. Common underlying medical conditions included diabetes (33%), structural lung disease (22%) and congestive heart failure (12%). The most common indications for antibiotics were urinary tract infection (12%), skin & soft tissue infection (8%) and community-acquired pneumonia (7%). The most frequently prescribed antibiotics were 3rd generation cephalosporins (41%), parenteral vancomycin (37%) and cefepime (28%, a 4th generation cephalosporin not available in the UK). The majority of people (1,176/1,488; 79%) received more than 1 antibiotic during their hospital stay. The median duration of treatment for antibiotics was 7 days.

A total of 324 adverse events (AEs) were reported, with 298 people (20%) experiencing at least 1 antibiotic-associated AE. Using local antimicrobial guidelines, the investigators determined that 287 (19%) of the antibiotic regimens were not clinically indicated. The most common reasons for this were treatment of asymptomatic bacteriuria or treatment of non-infectious lower respiratory tract conditions (for example, aspiration pneumonitis and congestive heart failure). Of the 287 antibiotic regimens that were not clinically indicated, 56 (20%) were associated with an AE. The investigators calculated that for every additional 10 days of antibiotic treatment the risk of an AE increased by 3%.

Just over half of the events were 30-day AEs (186/324; 57%), with a median time to onset of 5 days. The most common 30-day AEs were gastrointestinal (42%), renal (24%) and haematologic abnormalities (15%). In total, 138 AEs (43%) were classed as 90-day AEs, of which 54 (39%) were C. difficile infections and 84 (61%) multidrug-resistant organism infections. Nearly all the antibiotic-associated AEs were considered clinically significant by the investigators (314/324; 97%). No deaths were attributed to an antibiotic-associated AE.

The rate of C. difficile infection for people receiving antibiotics was 3.9 (95% confidence interval [CI] 3.0 to 5.2) per 10,000 person-days. The antibiotics most frequently associated with C. difficile infection were 3rd generation cephalosporins, cefepime and quinolones. The rate of incident multidrug-resistant organism infection was 6.1 (95% CI 4.9 to 7.6) per 10,000 person-days. Subsequent gram-positive resistance was observed in 60 people (4%), most of which (67%) was related to vancomycin-resistant enterococci infections. Gram-negative resistance occurred in 30 people (2%), with extended spectrum beta-lactamase production the most common resistance mechanism.
Commentary
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The Tamma paper is an important study that highlights the often forgotten downside of antimicrobial therapy: patient harm. There has been plenty of awareness of harm by single antimicrobial class (for example quinolones and tendinopathy) or by infection syndrome (for example otitis media antibiotic treatment and adverse events, with a number needed to harm [NNH] of 14, NICE CKS), but we have not had an overview of the combined harm for hospital inpatient settings to date.

Whilst this is a single centre retrospective study looking at only 4 adult medical wards over a 10 month period in a tertiary USA hospital, the results are probably applicable to UK hospitals, despite different proportions of antibiotic classes being used. The bottom line is 1 in 5 patients are being harmed by antibiotic use during the subsequent month (or three months for serious harms such as Clostridium difficile infection or multidrug resistant organisms).

Importantly, the study highlighted that 19% of the patients who were harmed did not require the antibiotics. In line with the Public Health England (PHE) hospital antimicrobial stewardship tool ‘Start smart then focus’, antibiotics should only be started where evidence of bacterial infection exists and to ensure that review of empiric antibiotics occurs within 48 to 72 hours of initiation. Sending appropriate samples for culture is paramount to maximise the evidence to help de-escalate or cease inappropriate therapy. Data on the outcome of day 3 review in England (PHE Antimicrobial Resistance [AMR] Fingertips) shows a low stop or change percentage despite an AMR CQUIN to improve this.

The paper highlights that increasing antibiotic exposure was linked to increasing adverse drug events; that is a 3% increase per 10 day course. Whilst most AEs occurred during the hospital stay, almost a quarter occurred after discharge. The paper also highlights higher hospital costs through increased length of stay, hospitalisation, additional out-patient appointments or laboratory tests.

In summary, this paper highlights the need to ensure that antibiotic use is carefully balanced between need and avoiding possible harm and unnecessary hospital costs or stay.

Declaration of interests:
In the past 12 months Philip Howard has received travel and accommodation payments from Alere Ltd and is a trustee of the British Society of Antimicrobial Chemotherapy (Vice President) and the UK Clinical Pharmacy Association.

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References
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