The epidemiology of antimicrobial resistance in hospital acquired infections: problems and possible solutions

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Hospitals, and particularly intensive care units, are an important breeding ground for the development and spread of antibiotic resistant bacteria. This is the consequence of exposing to heavy antibiotic use a high density patient population in frequent contact with healthcare staff and the attendant risk of cross infection.[1 2] Antibiotic resistance increases the morbidity and mortality associated with infections and contributes substantially to rising costs of care resulting from prolonged hospital stays and the need for more expensive drugs.[1–3] In this review I will outline the current problems caused by major drug resistant nosocomial pathogens, examine factors that promote antibiotic resistance in hospitals, and discuss strategies for control.

Summary points

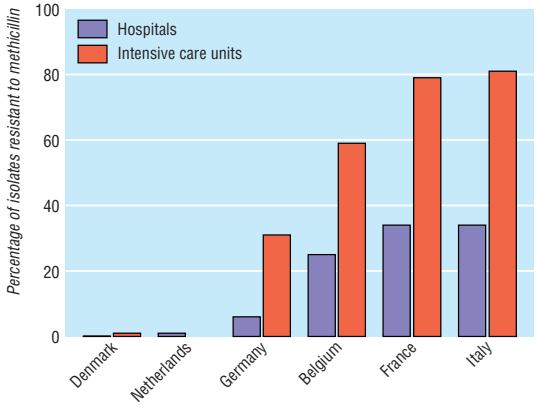
- The increasing incidence of hospital acquired infections caused by antibiotic resistant pathogens has led to an increase in morbidity and mortality
- Resistance results from the interplay of micro-organisms, patients, and the hospital environment, including antibiotic use and infection control practices
- An important cause of increasing antibiotic resistance is the selection of resistant bacterial strains by mutation and transfer of mobile resistance genes as a result of excessive antibiotic prescribing by hospital doctors
- Increasing antibiotic resistance is also caused by transmission of resistant bacteria within hospitals by cross colonisation of patients via the hands of healthcare staff and subsequent spread between hospitals by transfer of colonised patients
- Strategies to control antibiotic resistance in hospitals include multidisciplinary cooperation in implementing local policies on use of antibiotics and infection control measures, timely detection and reporting of the antibiotic resistant strains, improved surveillance, and aggressive control of transmission of epidemic resistant bacteria

The rise in antimicrobial resistance

Among pathogens causing hospital infections, Gram positive cocci have become predominant over the past two decades. This trend is related to these pathogens' capacity for accumulating antibiotic resistance determinants.[2] A notable example is that of methicillin resistant strains of *Staphylococcus aureus* (MRSA), which emerged in the 1970s and increased in frequency as hospital pathogens during the 1980s and '90s in many countries—with the notable exception of the Scandinavian countries and the Netherlands (figure).[4–7] Countries with lower incidence of MRSA infections tend to be more restrictive in antibiotic use, to apply strict infection control measures, and to have better ratios of nurses to patients in their healthcare institutions.[6] The rise in MRSA infections was initially associated with epidemics in large teaching hospitals, later spreading to the general hospitals and nursing homes.[7] Control stategies, such as contact isolation precautions (for example, systematic use of gloves, gowns, and hand antisepsis for care procedures) and carrier decolonisation with topical antimicrobials, met with varying degrees of success but seemed at least to slow down transmission.[6–8] Most MRSA strains are resistant to most other antibiotics, thereby necessitating the use of glycopeptide antibiotics, such as vancomycin. Recently, treatment failures caused by some strains with decreased susceptibility to vancomycin (vancomycin intermediate *S aureus* (VISA)) were reported in Japan and the United States.[9 10] Infections caused by these strains leave very few therapeutic options, and their emergence therefore adds to the rationale for containing MRSA transmission and restricting vancomycin use in hospitals.[10]

Enterococci, commensal inhabitants of the intestinal and genital tracts, are rising in prominence as hospital pathogens.[2] This rise is related to their natural resistance to most commonly used antibiotics and their capacity to acquire resistance to other antibiotics either by mutation (penicillins) or by transfer of resistance genes on plasmids and transposons (aminoglycosides and glycopeptides).[2 3] In the United States acquired vancomycin resistance has increased more than 20-fold among nosocomial isolates of enterococci, from 0.3% in 1989 to 10% in 1995.[2] This rise paralleled a massive increase in the use of vancomycin in US hospitals and was associated with spread of resistance plasmids and transposons among multiple strains of *Enterococcus faecium* and *E faecalis*.[2 11] In addition, epidemics of infection with vancomycin resistant enterococci broke out, initially in intensive care units and later in whole hospitals.[11–13] Most of these vancomycin resistant strains are resistant to all other effective antimicrobials. In patients with bacteraemia due to these strains, the mortality attributable to the infection is substantial.[14] In Europe the incidence of infection caused by multiple resistant enterococci remains lower, although several outbreaks have been reported in transplant and intensive care units.[15] About 2-5% of the population in Europe are intestinal carriers of vancomycin resistant *E faecium*, presumably acquired from the food chain.[16]

Multiple antibiotic resistance to useful classes of antibiotics, including the penicillins, cephalosporins, aminoglycosides, and fluoroquinolones, has gradually increased among a number of Gram negative hospital pathogens, especially *Klebsiella pneumoniae*,[2 17] *Entero-*



Proportion of *S aureus* isolates resistant to methicillin recovered from clinical specimens of inpatients in selected European countries. Data for hospitals are derived from Voss et al,[4] and data for intensive care units from Vincent et al[5]

bacter spp,[18 19] *Pseudomonas aeruginosa*,[20] and *Acinetobacter baumannii*.[21 22] Epidemic and endemic infections caused by these multiple resistant strains followed intense antibiotic use in many hospitals, particularly in intensive care units.[2 18 20 22 23] In a recent European hospital survey 23% of isolates of Klebsiellae were resistant to third generation cephalosporins by production of plasmid encoded extended spectrum β lactamases.[17] In many cases, epidemic strains of these Gram negative bacilli showed resistance to nearly all available antibacterial drugs and caused serious nosocomial infections —such as pneumonia and bacteraemia—which were associated with increased mortality.[18–21 24] The implementation of contact isolation measures for colonised patients or the modification of policies on antibiotics to curtail the massive use of drugs associated with these outbreaks, or in some cases both of these measures, were generally effective control measures.[2 20–22]

In addition to this increasing resistance among common agents of nosocomial infection, transmission of community acquired pathogens (such as multiple resistant *Mycobacterium tuberculosis* and *M bovis*) was observed in recent years in the United States and Europe in institutions caring for patients infected with HIV.[25] This underlined the need for appropriate diagnostic and treatment facilities for these patients, including respiratory isolation facilities in hospitals.[26]

Factors promoting antimicrobial resistance

The first steps that contribute to the increasing incidence of hospital acquired infections caused by antibiotic resistant pathogens are the selection of resistant mutant strains from the patient's own flora during antibiotic treatment or the transfer between bacteria of mobile genetic determinants of resistance (plasmids and transposons).[2 3 11 20] Subsequently, resistant strains spread among patients in hospital.[1 2 3 7 11 12 19–21] Selection of resistance in infecting or colonising bacteria is enhanced by factors related to the patient: immune suppression, infection of foreign bodies that impede local host defences, or presence of a large bacterial inoculum as reservoir of resistant mutants.[1 2 3 7 20 21] Other predisposing factors depend on the medical management: use of monotherapy rather than combination therapy may favour selection of resistance in certain infections, as will insufficiently high drug doses or an inappropriate route of administration, which may fail to achieve bactericidal drug levels at the site of infection.[2 3 20] Alteration of the endogenous microflora during antibiotic treatment also enhances replacement of susceptible organisms by resistant strains from the hospital microflora. Most commonly, transmission occurs as a result of contact between patients via the contaminated hands of healthcare staff.[1 2 7 19–21] Factors predisposing to this transmission include the length of stay in hospital, intensity and duration of exposure to broad spectrum antibiotics, severity of underlying illness, use of invasive devices such as intravenous catheters, or surgery.[1 7 20 21 24] Outbreaks with a common source of multiple resistant bacteria, often caused by organisms such as *Pseudomonas* spp and *Acinetobacter* spp, are another hazard. These are related to direct exposure of patients to contaminated food, equipment, or fluids—for example, during invasive procedures such as mechanical ventilation or endoscopy.[1 7 20 21]

The driving force of antibiotic resistance is the widespread use of antibacterial drugs. More than half of patients in acute care hospitals receive antibiotics as treatment or prophylaxis. Hospital doctors often prescribe antibiotics excessively and inappropriately, as shown in many studies.[27] Insufficient training in infectious diseases and antibiotic treatment, difficulty of selecting the appropriate anti-infective drugs empirically, insufficient use of microbiological information, need for self reassurance, and fear of litigation are prompting the use of broad spectrum drugs.[27] Likewise, compliance of healthcare staff with basic infection control practices—such as hand washing or disinfection—is incomplete, and shortage of healthcare staff often makes isolation precautions difficult to implement.[28]

Strategies for control

Several societies have published guidelines for optimising antibiotic use and curtailing antibiotic resistance in hospitals.[27 29 30] Key components of these guidelines include multidisciplinary coordination between hospital administrators, clinicians, infectious diseases specialists, infection control teams, microbiologists, and hospital pharmacists; formulary based local guidelines on anti-infective treatment; education and regulation of prescriptors by consultant specialists; monitoring and auditing of drug use; surveillance and reporting of resistance patterns of the hospital flora; detection of patients colonised with communicable resistant bacteria and notification of these to the infection control team when isolation of the patient or decolonisation, or both, would be useful; promotion and monitoring of basic hospital infection control practices such as hand hygiene. These guidelines are based more on expert opinion and on the results of descriptive and analytical studies than on evidence from controlled trials, which are difficult to design to evaluate these types of population based intervention. Each hospital has its own ecosystem and microsociety, where determinants of antibiotic resistance are quite specific, and therefore

effective solutions will need to be tailored to local epidemiological circumstances and resources.

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Community acquired infections and bacterial resistance

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In this paper we review the problems of antibiotic resistance in community acquired infections. We discuss pathogens that have a large impact on morbidity and mortality in the community such as *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Neisseria meningitidis*, the enteric pathogens *Salmonella* spp and *Campylobacter* spp, and the urinary tract pathogen *Escherichia coli*.

Summary points

- The frequency of resistance to antibiotics among community acquired pathogens and the number of drugs to which they are resistant is increasing
- Resistance to antimicrobial drugs has been clearly linked to consumption of antibiotics
- The boundaries between community and hospital environments are becoming more blurred and this may have consequences for the development of resistance to antimicrobial drugs
- Strategies to limit the spread of resistant strains should include encouraging the judicious use of antimicrobial agents
- Guidelines should be based on results derived from well designed surveillance studies

Streptococcus pneumoniae

Infection with *S pneumoniae* is the biggest cause of potentially life threatening, community acquired diseases such as meningitis and pneumonia. It is also the leading bacterial cause of otitis media and sinusitis. However, this pathogen has evolved to reach unexpected levels of resistance to antibiotics. Before the early 1990s most pneumococci isolated in the European Union and the United States were susceptible to penicillin, with minimum inhibitory concentrations of <0.1 mg/l[1]; this concentration of penicillin killed these organisms rapidly. Since then, resistance to