International Journal of Antimicrobial Agents 36S3 (2010) S3–S7

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

The continuing crisis in antibiotic resistance

G.L. French*

Department of Infection, King's College and Guy's & St Thomas' Hospital, London SE1 7EH, UK

ARTICLE INFO

Keywords:
Antibiotic resistance
Clostridium difficile
Enterococci
Escherichia coli
Infection control
Staphylococcus aureus

SUMMARY

The emergence of antibiotic resistance in bacterial pathogens is an inevitable consequence of antibiotic use. Despite repeated warnings, negligent antibiotic use and poor infection-control practice have led to the continuing development of extensive resistance problems worldwide. Multidrug-resistant pathogens are now characterized by their heterogeneity, increasing virulence, resistance even to reserve agents and spread within and between hospitals and the community. Examples are glycopeptide-resistant meticillin-resistant *Staphylococcus aureus* (MRSA) and enterococci, extended-spectrum β-lactamase- and carbapenemase-producing coliforms, and toxin-hyperproducing *Clostridium difficile*. Effective national and international programmes of control to combat these problems are urgently needed. The potential for success of such coordinated efforts has been demonstrated by the recent dramatic reductions in MRSA and *C. difficile* infections in England.

Introduction

When Fleming discovered penicillin he observed that some bacteria were inherently sensitive and others inherently resistant [1]. In his Nobel lecture he also noted that initially sensitive bacteria could develop resistance, especially if exposed to low doses, and warned that if penicillin were to become cheap and easily available, 'negligent' use might encourage resistance and failure of therapy [2].

The tendency for antibiotic use to promote the emergence of resistant pathogens is called antibiotic pressure, and there are many reports of resistance rising during increased antibiotic use and falling after a reduction in use [3]. Although most antibiotic use is within the community, the greatest concentration of use per patient is in hospitals, and hospital pathogens tend to be the most resistant. The first bacterial response to increasing antimicrobial pressure is the displacement of inherently antibiotic-susceptible species – or relatively sensitive strains within a species – by inherently more resistant organisms, so that the proportion of strains with decreased susceptibility rises. This tends to favour firstly the emergence within hospitals of free-living opportunistic pathogens that are relatively antibiotic resistant, probably because of their exposure to natural antibiotics in the environment. Secondly, inherently sensitive organisms begin to acquire new, usually high-level, resistance mechanisms, a process that is accelerated when these mechanisms are encoded on transferrable plasmids and transposons. Acquired resistance is particularly important for the more virulent human pathogens, which often obtain their new resistance genes from less virulent environmental organisms. This change from more susceptible to more resistant populations is an inevitable evolutionary response to antibiotic usage and has occurred rapidly because of the short bacterial generation time.

A change in the pattern of serious hospital infection after the introduction of antibiotics was first noted early in the antibiotic era. Between 1935 and 1957, antibiotic-sensitive Gram-positive pathogens were replaced as a cause of serious hospital infections by inherently penicillin-resistant Gram-negative bacteria such as *Escherichia coli*, *Klebsiella* and *Proteus* spp. [4], and penicillin-sensitive *Staphylococcus aureus* were soon replaced in hospitals by resistant strains [5]. From the 1960s to the 1980s a range of new antimicrobials were introduced to combat emerging resistance. The worldwide problem of the multidrug-resistant (MDR) 'hospital staphylococcus' in the 1960s diminished after the introduction of meticillin and other penicillinase-stable penicillins [5]; outbreaks of gentamicin-resistant *Klebsiella* and other Gram-negative organisms seen in the 1970s waned in the 1980s with the use of newer aminoglycosides, cephalosporins and quinolones. The pattern then changed again with the emergence of MDR Gram-positive hospital pathogens such as multiresistant *S. aureus* and coagulase-negative staphylococci and enterococci.

Antibiotic usage has continued to select pathogens resistant to newer antimicrobials and agents considered to be treatments of last resort. These include enterococci and, to a lesser extent, meticillin-resistant *Staphylococcus aureus* (MRSA) resistant to glycopeptides, and Gram-negative bacteria with inherent (*Stenotrophomonas* spp.) or acquired (*Pseudomonas, Acinetobacter* and enterobacterial species) resistance to carbapenems. Broad-spectrum antibiotic use has also encouraged the emergence of new, highly virulent strains of antibiotic-resistant *Clostridium difficile* that cause diarrhoea and pseudomembranous colitis.

* Correspondence: Tel.: +44 (0)207 188 3127.
E-mail address: gary.french@kcl.ac.uk (G.L. French).

0924-8579/$ – see front matter

Hospital infection is now microbiologically heterogeneous, being caused simultaneously by many different species of MDR Gram-positive and -negative bacteria. Furthermore, the boundary between hospital and community pathogens is becoming increasingly blurred, with similar MDR pathogens (especially MRSA, glycopeptide-resistant enterococci, extended-spectrum β-lactamase-producing *E. coli* and virulent strains of *C. difficile*) causing both hospital- and community-onset infections.

Multiresistant problem organisms

Escherichia coli and other enterobacteria

Escherichia coli does not survive well in the environment and, until recently, caused mainly endogenous infection from the patient's own bowel rather than cross-infection or person-to-person spread. The species is naturally susceptible to ampicillin, but now about 50–60% of both hospital and community isolates are resistant, usually by the production of TEM1 or TEM2 β-lactamases [6,7]. Mutations in *TEM1* and *TEM2* have resulted in new, extended-spectrum β-lactamases (ESBLs) that render *E. coli* resistant to the second- and third-generation cephalosporins. The genes encoding these enzymes are usually borne on transferrable plasmids and are often associated with aminoglycoside and other resistances.

However, nosocomial infections and outbreaks involving MDR coliforms have usually been caused by *Klebsiella* spp. and, to a lesser extent, *Enterobacter* and *Serratia* spp. Until recently, *E. coli* has remained generally antibiotic-sensitive (apart from resistance to ampicillin) and has not caused much cross-infection or spread within hospitals or the community. This situation changed with the worldwide emergence in the 1990s of *E. coli* that produces CTX-M and ESBLs [8,9]. Compared with other ESBLs, CTX-M enzymes are more active against cefotaxime than against other third-generation cephalosporins; they appear to have originated from the *Kluyvera* spp. of environmental bacteria and more than 50 different types have been identified. They are encoded in transferrable transposons and plasmids and have disseminated widely among enterobacteria. CTX-M-producing *E. coli* are usually also resistant to the aminoglycosides and quinolones and appear to be highly transmissible, both in the community and in hospitals. Most isolates are clonally unrelated but large single-strain community outbreaks occur [10]. Increasing asymptomatic faecal carriage suggests that these organisms may be spread by food sources and international travel.

The world pandemic of CTX-M-producing *E. coli* has resulted in a new epidemiology for MDR coliforms [11]. Opportunistic hospital outbreaks with mainly single clones of SHV- and TEM-type ESBL-producing *K. pneumoniae* have been replaced by sporadic and epidemic community infections with heterogeneous clones of more virulent MDR CTX-M-producing *E. coli.* Spread occurs among healthy elderly people at home and in long-term care facilities; admission of these groups to hospitals or care homes may result in nosocomial outbreaks. The common presentation is urinary tract infection (sometimes complicated by bacteraemia) in catheterized, elderly, community or newly-admitted hospital patients.

There were about 22 000 episodes of *E. coli* bacteraemia in England, Wales and Northern Ireland in 2007 [12]. Resistance to third-generation cephalosporins in *E. coli* blood isolates increased from about 2% in 2001 to 12% in 2007; resistance to ciprofloxacin rose from 1% to 23% and to gentamicin from 1% to 8.5%. Resistance to carbapenems was rare (≤0.2% in 2007). There were 6000 episodes of *Klebsiella* bacteraemia in 2007; 14% resistant to third-generation cephalosporins (up from 4% in 1994), 15% to ciprofloxacin and 10% to gentamicin (resistance to carbapenems was not reported). Thus multiple antibiotic resistance in blood isolates of *E. coli* in UK hospitals in 2007 was similar to or higher than that in *Klebsiella* isolates and *E. coli* was isolated 3.7 times more frequently than *Klebsiella*.

Carbapenems are now the treatment of last resort for MDR coliforms. The recent emergence of carbapenem resistance in these organisms is therefore a matter of concern. Carbapenem resistance in enterobacteria can be mediated by a variety of mechanisms, including the production of several different carbapenemases. Organisms producing carbapenemases are rare in most parts of the world, but there have been increasing reports of plasmid-mediated *K. pneumoniae* carbapenemase (KPC) in some parts of China, Israel, Greece, South America and the USA [13]. In addition, there have recently been reports of enterobacteria, particularly *E. coli* and *K. pneumoniae,* that produce a newly identified transmissible carbapenamase, New Dehli metallo-β-lactamase 1 (NDM-1) [14]. These organisms are uncommon but increasing and are often resistant to all available antimicrobials except tigecycline and colistin; they have been found in India, Pakistan and the UK, with evidence of intercontinental spread. It must be concluded that multiresistant coliforms are now a serious public health threat.

Meticillin-resistant Staphylococcus aureus

Strains of MRSA were noted soon after meticillin was introduced into clinical practice but were generally rare until the 1980s. In the late 1970s, however, MRSA emerged as a major pathogen of hospital infection worldwide [15]. In both the USA and Europe up to 30–50% of invasive hospital isolates of *S. aureus* are now meticillin-resistant [16,17], although in the Netherlands and Scandinavia rates are ≤3%.

Meticillin resistance is mediated primarily by the production of an abnormal penicillin-binding protein called PBP-2a or PBP-2′, which reduces the binding of all β-lactam drugs to the cell wall [18]. The production of PBP-2a is encoded by the *mecA* gene contained within the staphylococcal cassette chromosome *mec* (*SCCmec*). Clonal lineages of *S. aureus* can be characterized by their *SCCmec* and multilocus sequence type and this has shown that MRSA has repeatedly emerged from meticillin-sensitive *S. aureus* (MSSA) at different times in different parts of the world [19,20].

Until recently, MRSA infections were predominantly hospital-acquired or caused by strains acquired during previous hospital or healthcare contact (HA-MRSA). True community-associated MRSA (CA-MRSA) began to appear in the 1990s in patients without prior healthcare contact [21]. These CA-MRSA clones appear to have emerged in community strains of MSSA by acquisition of the SCC*mec* cassette. HA-MRSA tends to cause infection in hospitalized, compromised, elderly patients, often with a history of surgery or indwelling devices and prior antimicrobial therapy, and rarely causes primary infection in healthy people. By contrast, CA-MRSA has the virulence of its MSSA parents, affects younger, healthy people and spreads readily in community settings and hospitals. CA-MRSA is characteristically susceptible to most non-β-lactam antimicrobial agents, contains SCC*mec* types IV or V and produces the Panton–Valentine leukocidin toxin (PVL), a putative virulence factor that has been associated with severe skin sepsis and fatal necrotizing pneumonia. However, CA-MRSA does cause hospital outbreaks and some strains are developing multiple resistance [22].

CA-MRSA is now common in the USA, and in some US cities is a more frequent cause of infection in both hospitals and the community than either HA-MRSA or MSSA [23]. CA-MRSA is much less prevalent in Europe but rates are increasing. CA-MRSA infections in the USA are caused predominantly by the PVL-positive USA300 strain, but elsewhere CA-MRSA strains are more heterogeneous and only about half express PVL [24].

The shuttling of CA-MRSA between hospital and community may result in more frequent MRSA infections in the community, more