Meeting the challenge of healthcare-associated infections with new antimicrobials: with a focus on Clostridium difficile

Healthcare-associated infections (HCAI), previously known as hospital acquired infections (HAI), are defined as infections resulting from medical care or treatment in hospital. HCAI may be caused by any infectious agent from endogenous or exogenous sources and affect any part of the body. Five infections: central line-associated blood stream infection, catheter-associated urinary tract infection, surgical site infection, Clostridium difficile infection and healthcare associated pneumonia account for 85% of HCAI[1].

By Professor Peter Hawkey and Dr Katie Hardy

Gathering accurate data on the number of HCAI occurring each year is problematic, but it is estimated by Centers for Disease Control and Prevention (CDC) that in the US there are approximately 1.7 million HCAI each year leading to 99,000 deaths[2]. While in 2004, the Department of Health confirmed approximately 300,000 HCAI occurred in the UK per year[3]. In terms of costs it is estimated that in the US HCAI result in additional healthcare costs of $28-33 billion dollars annually, and the cost to the NHS in the UK is thought to be in excess of £1 billion a year[4].

Any pathogen may cause HCAI, but bacteria are the most common cause, with much emphasis being placed on bacteria that are resistant to antibiotics, especially methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin resistant *enterococci* (VRE), multi-drug resistant Gram negative bacilli and *C. difficile*. While overall data on prevalence of HCAI is approximate, more accurate data is available for specific organisms in some countries. The European prevalence of MRSA from bloodstream infections has been monitored through the European Antimicrobial Resistance Surveillance Network (EARSS) and has demonstrated that, in the early 2000s, MRSA accounted for >25% *S. aureus bacteraemias* in many central and Southern European countries[5]. However, over subsequent years rates of MRSA bacteraemias have fallen in many countries across Europe, and in 2008 more countries demonstrated decreasing, rather than increasing, trends. Large reductions were observed in England and Wales, where from 2001 mandatory reporting of all cases of MRSA bacteraemia was introduced and targets

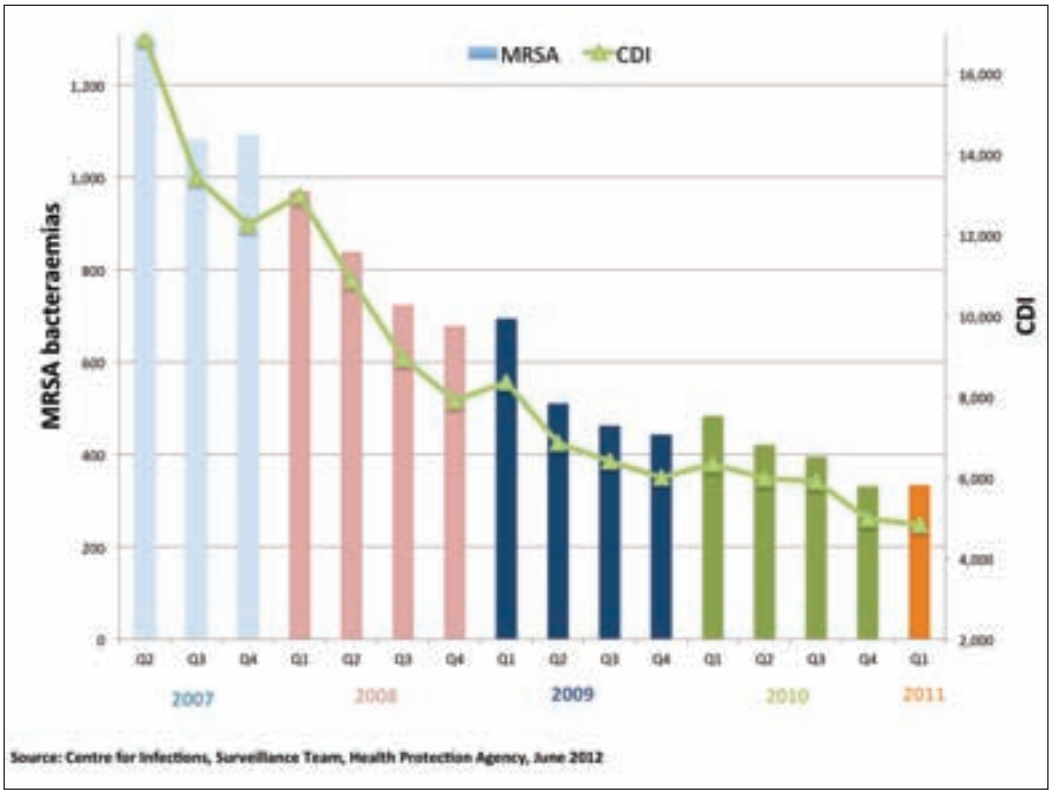

Figure 1
Trends in HCAI (MRSA and CDI) in England (2007-11).
Source: Centre for Infections, Surveillance Team, Health Protection Agency, June 2012

for reduction set (**Figure 1**). The proportion of *S. aureus* from blood that were methicillin-resistant decreased from 31% in 2007 to 19.3% in 2009. Decreases have also been observed in the US, with hospital onset invasive MRSA decreasing by 9.4% per year between 2005 and 2008[6].

All patients are at risk of acquiring a HCAI, but some patients are more susceptible due to their age, underlying disease, immunosuppression, medical interventions that they are receiving for example surgery or admission to intensive care, length of hospital stay and prescribing of antibiotics. The widespread use of antibiotics can affect HCAI in two ways, firstly by selecting for bacteria that are resistant to the antibiotics and secondly by altering the body's normal gut flora, enabling bacteria such as *C. difficile* to predominate and cause infection.

The acquisition of HCAI can occur in several ways, it can be endogenous, occurring from the patient's own flora entering the body, this is most likely with urinary tract infections or surgical site infections. Some HCAI are acquired from the environment, this is most likely with *Pseudomonas*, *Acinetobacter* and *Aspergillus* spp, which is more likely in ICU patients or those receiving chemotherapy. The other most likely exogenous source is other patients and then transfer via either healthcare staff or contamination of the clinical environment.

C. difficile is a bacterial infection that can cause symptoms ranging from mild diarrhoea to life-threatening inflammation of the colon. Patients can be colonised with the bacteria with no symptoms, with illness most commonly occurring following use of antibiotics, and the prevalence being much higher in the elderly. The incidence of *C. difficile* infection (CDI) increased in the mid-2000s, but accurately describing the incidence is hindered by the different reporting requirements and variability in testing for CDI[7]. In 2004 the NHS in England introduced mandatory reporting of all CDI cases, and while this still has limitations regarding comparability of data due to different testing methodologies, it has demonstrated a decrease in CDI cases of 73.3% from 2007/08 to 2011/12 (**Figure 1**)[8,9]. A study in 2008 in 97 hospitals from 34 European countries demonstrated a wide variation in prevalence per 10,000 patient days from 0.3 to 19.1 cases, with an aggregate rate of 4.1 cases per 10,000 patient days[10]. In the US rates have doubled over the last decade, with 76.9 episodes of CDI per 10,000 discharges being reported in 2005[2]. The rise in cases of CDI is partly attributable to the rise in an epidemic strain, ribotype 027 (Pulse field gel type NAP1), with large outbreaks occurring in North America and Europe. Between 2001 and 2003 large outbreaks

were observed in Quebec, with 82% of the strains responsible being ribotype 027. In the UK in 2003/04, 334 patients acquired *C. difficile* at one hospital with 33 deaths attributable to CDI, which was the first major 027 outbreak. In the UK there has been rapid access to a ribotyping service (*C. difficile* ribotyping network, CDRN) since 2007. Isolates of *C. difficile* submitted to the CDRN are from severe cases, clusters or if an increase in incidence has been observed, so although this gives an indication of the ribotypes causing disease, the sampling frame is incomplete (~22%) and potentially biased. From 2007 until 2010, 11,294 isolates have been ribotyped by CDRN, with ribotype 027 predominating, but decreasing markedly from 55% in 2007/08 to 21% in 2009/10 and there being large regional variations. In England, there has been a substantial decrease in the incidence of CDI, much of which can be attributed to the decrease in 027. The distribution of ribotypes is now much broader, with no individual ribotype predominating. As has been demonstrated by other studies, CDRN data shows that ribotype 027 was associated with increased mortality.

Control of HCAI is multi-factorial, with different factors needing to be considered, including patient case mix, patterns of healthcare delivery, the environment, diagnostic interventions and antimicrobial stewardship[11]. Measures that have been introduced have been both general and therefore effective in reducing all healthcare-associated infections, for example hand hygiene campaigns and improving environmental cleanliness, but also specific for example care bundles for central lines and urinary catheters. The effectiveness of the various infection control measures that have been introduced varies, with one study demonstrating a lower MRSA rate linked to hand hygiene and isolation and a lower rate of CDI to cleanliness and good antimicrobial prescribing practices[12]. Several studies have demonstrated that reduction in the use of cephalosporins and fluoroquinolones has lead to a decrease in the incidence of CDI[13].

The therapy of *Clostridium difficile* infection is complicated by a number of factors. Firstly, the pathogenesis of the disease is complex as the development of the disease is largely dictated by the patient's immune response to *C. difficile* in the gut, the exposure of patient both to precipitating antibiotics (eg, clindamycin, cefotaxime, ciprofloxacin, etc) and the response of the patient's host flora to those antibiotics. A further complication is that different clones of *C. difficile* may become important epidemic strains if they acquire novel resistance to antimicrobials that are widely used in the setting where susceptible patients are being managed. Another level of complexity occurs because of the difficulty of making a definitive diagnosis. No single test can be relied upon to provide an unequivocal diagnosis[14]. In consequence many trials and also epidemiological studies are dogged by poorly-defined patients. This is particularly true when studies are carried out in low incidence settings where some of the tests particularly enzyme immuno assay (EIA) tests for toxin have a high false positive result rate which results in patients without true disease being included in treatment or comparator arms[15].

The current treatments (metronidazole and vancomycin) have a high relapse rate and therefore there is a strong motivation to identify improved therapeutic agents for treating CDI. A Scottish study of *C. difficile* isolates from 1979 to 2004 demonstrated high levels (>90%) of resistance to clindamycin and the emergence in 1994-2004 of moxifloxacin resistance (10%), which was 0% in 1979 to 1986[16]. Another Scottish study of isolates from 2007 to 2009 showed high levels of resistance to moxifloxacin (>96%) in only the epidemic ribotypes 027, 106 and 001[17]. This finding is similar to a recent survey from the US (2008-09) when 97% of 027 strains were moxifloaxcin resistant[18]. The widespread use of fluoroquinolones was rapidly linked to the epidemic of ribotype 027 and the heavy use of those agents. It is certainly clear that ribotype 027 typically carries high level resistance to fluoroquinolones as well as resistance to other antibiotics[19,18]. There have been two systematic reviews of antibiotic treatment for CDI in adults. One review reported superiority of teicoplanin over vancomycin and metronidazole[20]. This was based on three small studies of relatively low power and with a high risk of bias and requires further confirmation. The second review from the USA (no assessment of teicoplanin, presumably because it is not licensed) concluded that the strength of evidence regarding comparative effectiveness and harms of treatment for CDI was generally low to moderate and that only a few clinical trials are available to establish an evidence base[21]. They found moderate strength evidence that metronidazole, vancomycin and fidaxomicin were effective for initial cure and that no agent was clearly superior using this endpoint. Recurrence was lower in the large fidaxomicin study they considered and that the evidence was of moderate strength[22]. These results were replicated in a later phase III study of fidaxomicin which was not included in the review[23]. In a pooled analysis of patients taking concomitant antibiotics and were enrolled in the

two Phase II fidaxomicin studies[23,22], Mullane et al reported a higher rate of recurrence in all patients treated with concomitant antibiotics, although this was lower in the group treated with fidaxomicin[24]. In patients receiving no concomitant antibiotics at any time (ie during treatment or follow up period), recurrence was significantly lower in the group treated with fidaxomicin than vancomycin ($P < .0010$). A review of 69 publications also showed a lower recurrence rate with fidaxomicin, but no studies had metronidazole as a comparator[25]. In the case of a study which purports to show that vancomycin is superior to metronidazole in severe disease this is entirely dependent upon the author's protocol and modified intention to treat analysis which showed moderate superiority of vancomycin to metronidazole, but on the strict intention to treat analysis there is no significant difference in the percentage of patients initially cured[26]. Having said this, most clinicians now use vancomycin in severe disease and unfortunately this prescribing practice has trickled down into moderate and mild disease with a potential for the selection of vancomycin resistant *enterococci* in the flora of the patient for which evidence for and against exists[27].

There are a number of pre-clinical investigational drugs and those that have come to evaluation which are either not being actively progressed at the moment or have been withdrawn from development. A useful review of some of these agents is presented by McFarland and colleagues and include ramoplanin, the toxin binding absorbents synsorb which was abandoned following a failure to demonstrate a difference to placebo and tolevamer (another toxin absorbant) which was also shown to have a significantly poorer outcome when compared to vancomycin and metronidazole in Phase III studies[28]. Nitazoxmide is also not being actively developed currently as again in a Phase III study no significant advantage over metronidazole was demonstrated[28]. Glycopeptides, other than vancomycin have been investigated and recent studies with oritavancin suggest there might be some advantages over vancomycin. In a hamster model orally administered oritavancin was shown to be more effective than vancomycin[29]. Rifampicin has been used for either adjunctive therapy in an attempt to reduce recurrence or in the case of rifaximin has a primary treatment. A randomised double blind placebo controlled study demonstrated that patients with CDI given a rifamixin chaser regime experienced a decrease in recurrent diarrhoea compared with the administration of a placebo[30]. A number of optimistic reports with rifampins are both theoretically and actually undermined by the selection of rifampin resistant *C. difficile* isolates and in the case of one report the pre-existing occurrence of a rifampicin-resistant clone in a large hospital in the USA[31]. The glycylcyline tigecycline has also been suggested and shown *in vitro* studies to have activity against CDI, with a number of case reports demonstrating good outcomes[32]. Not surprising though that there has been a case report of failure of tigecycline to treat a severe CDI which means that caution must be expressed in pursuing tigecycline as a practical drug particularly in view of the fact only very limited data exists for use of CDI as a primary therapy[32]. A number of reports have shown that the oxazolidinone antibiotic linezolid has *in vitro* activity against *C. difficile* and a programme to produce analogues has resulted in the recent report of a novel biaryl derivative RBx 11760[33]. The authors demonstrated in a hamster model superiority to vancomycin with MIC susceptibility studies demonstrating up to a 16-fold increase in activity compared to linezolid. While nitazoxmide is not being actively pursued, very recently a derivative has been described, amixicile, which in a mouse model while suggesting a lower initial clinical response ,there was a lower recurrence rate when compared to both vancomycin and fidaxomicin[34]. These are very preliminary data and suggest further evaluation of derivative of nitazoxmide may well be worthy of further development. A number of other novel agents are either being developed or evaluated to varying degrees of success and include REP 3123, a novel diaryldiamine that inhibits the methionyl-tRNA synthetase enzyme *C.difficile* with little damage to other members of the normal GI flora[35]. So far this agent has only been reported as its basic mode of action and range of antimicrobial activity. There are quite a range of antibiotics, which have been identified as potential leads for activity against *C. difficile*. One example would be reutericyclin which is produced by *lacto bacillus reuteri*[36]. These antibiotics have the advantage of good safety profile due to their failure to be absorbed into the gut (they are used in foods as preservatives), while often having highly specific targeted activity against gram positive bacteria. Bacteriocins have also been identified as being potentially useful for treating CDI notably that produced by the insect pathogen *Bacillus thuringiensis* which has been evaluated in a distal gut *in vitro* model, in which it demonstrated superior activity to both vancomycin and metronidazole[37]. Extending this theme insect peptides have also been investigated with a recent report of a peptide from the Korean dung beetle *Copris tripartitus*

which demonstrated not only significant activity in a mouse model against *C. difficile* but also potentially useful anti-inflammatory activity[38]. A novel potential therapeutic strategy is to interfere with host mediated activations of *C. difficile* toxins[39]. Researchers demonstrated that *C. difficile* toxins are S-nitrosylated by the infected host and that S-nitrosylation attenuates virulence by inhibiting toxin self-cleavage and cell entry. They developed a structural analogue of the enzymes concerned which induced conformational changes in the toxin and enabled host S-nitrosothiols to transnitrosylate the toxin catalytic cysteine which forms part of a structurally conserved nitrosylation motif. The authors believe this may represent a new avenue to therapeutic development in the field of treating CDI[39]. This review has identified some novel chemical entities for the treatment of *C. difficile* infection, but there is interest in vaccines with variable clinical trial results. The use of both probiotics is generally not proven, but replacement faecal bacterio-therapy has been reported to offer high cure rates, especially in relapse cases[40]. The development of novel therapies is always hard with seemingly endless licensing hurdles to be cleared, including the requirement for two Phase III randomised controlled trials with stringent guidelines for both the European Medicine Agency and the FDA. A lot of small biotech companies have identified potential hits and leads in this area, however often the relatively small market size of CDI therapy has resulted in products either being withdrawn or not progressing. There are a number of potential novel chemical entities which may well improve outcomes and importantly lower relapse rates in patients. The wider recognition of CDI in areas other than North America and Europe may well drive forward need for better treatments. DDW

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