J Antimicrob Chemother 2011; **66**: 1–14
doi:10.1093/jac/dkq415 Advance Access publication 16 November 2010

Journal of Antimicrobial Chemotherapy

Escherichia coli O25b-ST131: a pandemic, multiresistant, community-associated strain

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Escherichia coli sequence type 131 (ST131) is a worldwide pandemic clone, causing predominantly community-onset antimicrobial-resistant infection. Its pandemic spread was identified in 2008 by utilizing multilocus sequence typing (MLST) of CTX-M-15 extended-spectrum β-lactamase-producing *E. coli* from three continents. Subsequent research has confirmed the worldwide prevalence of ST131 harbouring a broad range of virulence and resistance genes on a transferable plasmid. A high prevalence of the clone (∼30%–60%) has been identified amongst fluoroquinolone-resistant *E. coli*. In addition, it potentially harbours a variety of β-lactamase genes; most often, these include CTX-M family β-lactamases, and, less frequently, TEM, SHV and CMY β-lactamases. Our knowledge of ST131's geographical distribution is incomplete. A broad distribution has been demonstrated amongst antimicrobial-resistant *E. coli* from human infection in Europe (particularly the UK), North America, Canada, Japan and Korea. High rates are suggested from limited data in Asia, the Middle East and Africa. The clone has also been detected in companion animals, non-companion animals and foods. The clinical spectrum of disease described is similar to that for other *E. coli*, with urinary tract infection predominant. This can range from cystitis to life-threatening sepsis. Infection occurs in humans of all ages. Therapy must be tailored to the antimicrobial resistance phenotype of the infecting isolate and the site of infection. Phenotypic detection of the ST131 clone is not possible and DNA-based techniques, including MLST and PCR, are described.

Keywords: β-lactamases, molecular epidemiology, bacterial infections

Introduction

Escherichia coli is a finely tuned, ubiquitous human pathogen. It is a common cause of urinary tract infection (UTI) and bacteraemia in humans of all ages. In addition, it is a frequent cause of varied organ infections, ranging from the biliary system to the CNS. The spectrum of pathology can range from a spontaneously resolving cystitis to life-threatening sepsis syndrome.[1] Not confined to the community, *E. coli* infection is also a common hospital-acquired pathogen.[2]

Over the past five decades, we have witnessed increasing antimicrobial resistance in *E. coli* in the community setting. Initially, resistance was described to particular agents, such as ampicillin, trimethoprim, sulphur-based antimicrobials or tetracyclines.[3] More recently, the horizon of resistance has broadened, with the emergence of broad resistance to large families of agents. In particular, plasmid-mediated extended-spectrum β-lactamases (ESBLs) have become prominent in community-onset *E. coli* infection.[4,5] In addition to the resulting resistance to most β-lactam antibiotics, ESBL producers are frequently also resistant to aminoglycosides and fluoroquinolones.

There are a variety of reasons for the increased prevalence of antibiotic-resistant *E. coli*. *E. coli* is an organism known for its mobile genome and propensity to exchange genetic material.[6] However, the dissemination of 'clonal' organisms harbouring resistance is also well documented. Clonal outbreaks of *E. coli* clinical infection previously described include 'Clonal Group A' (CGA) in North America[7] and O15:K52:H1 in multiple nations.[7,8] It is estimated that 10%–20% of all *E. coli* UTIs may be caused by a small set of clonal groups.[9] In 2008, two research groups analysing the population biology of ESBL-producing *E. coli* almost simultaneously described 'serogroup O25b, sequence type 131 (ST131)' occurring in multiple countries on three continents. This previously unremarkable molecular clone harboured a CTX-M ESBL gene and a larger armamentarium of virulence genes.[10,11] Since this discovery in 2008, research has retrospectively documented a 'pandemic' emergence amongst ESBL-producing and other antimicrobial-resistant clinical isolates in the middle of this decade. Previous to this, only sporadic isolates of this clone can be identified in multilocus sequence typing (MLST) databases and published series. The rapid and apparently boundless rise of the ST131 *E. coli* clone is the subject of this review.

Epidemiology

Human infection and colonization

Published research detailing the geographical distribution and antimicrobial resistance of human infection and colonization by *E. coli* ST131 are summarized in Table 1.

Table 1. Geographical distribution and antimicrobial resistance of *E. coli* ST131 in humans

Country/Region	Specific location	Date range of samples	Isolate source	Selection criteria used by study	Number of isolates	Percentage of isolates that were ST131 (*n*)	Percentage of ST131 that were community onset	Percentage of ST131 that were fluoroquinolone resistant	Percentage of ST131 that were SXT resistant	Percentage of ST131 that harboured ESBL
Multinational[11]	Europe, Canada and Middle East	2000–06	laboratory collection	ESBL CTX-M-15	43	42 (18)	0	NS	NS	100
Multinational[10]	Europe, Asia and Canada	NS	clinical isolates and laboratory collection	ESBL CTX-M-15	41	88 (36)	39	97	53	100
Multinational[45]	worldwide, excluding India/Pakistan and Bangladesh	2004–06	traveller returned from region; majority UTI	ESBL	84	19 (16)	NS	NS	NS	100
Europe[18]		2003–06	community-acquired UTI	fluoroquinolone resistant	148	24 (35)	100	100	NS	NS
Belgium[28]		2006–07	clinical isolates	ESBL CTX-M-15	43	72 (31)	90	NS	NS	100
Croatia[29]		2002–05	clinical isolates	ESBL CTX-M	12	42 (5)	NS	100	NS	100
France[23]		1994–2003	laboratory collection	ESBL	128	6 (8)	NS	NS	NS	100
France[23]	Tenon	2002–03	UTI	non-ESBL + B2 phylotype	129	3 (4)	NS	NS	NS	0
France[24]		2005	bacteraemia	3GC resistant	41	15 (6)	NS	NS	NS	100
France[25]		2006	community-onset UTI	ESBL	48	21 (10)	10	100	60	100
France[23]		2006–07	laboratory collection	ESBL	41	46 (19)	NS	NS	NS	100
France[26]	Paris	2006	stools from healthy volunteers	none	100	7 (7)	100	57	NS	0
Ireland[17]		2003–07	majority UTI	ESBL	371	<10	NS	NS	NS	100
Italy[22]	Rome	2006	bacteraemia and UTI	fluoroquinolone resistant + ESBL	18	61 (11)	NS	100	NS	100
Northern Ireland[16,109]	Belfast	2004–06	stool samples from residents of LTCFs	ESBL + fluoroquinolone resistant	119	≥54 (≥64)	0	100	NS	100
Norway[27]		2003	clinical isolates	ESBL	45	20 (9)	NS	NS	NS	100
Spain[19]		2004	clinical isolates	ESBL	91	9 (8)	NS	NS	NS	100
Spain[61]	Madrid	2004–07	majority UTI	Amp-C	121	6 (7)	NS	NS	NS	0
Spain[20]		2006	clinical isolates	ESBL CTX-M-15	37	86 (32)	NS	NS	NS	100
Spain[21]	Lugo	2006–07	majority UTI	ESBL	105	22 (23)	NS	>96	>96	100
Spain[21]	Lugo	2007–08	majority UTI	ESBL	249	22 (54)	<50	NS	NS	100
Spain[106]	Madrid	2008	UTI	ESBL + fosfomycin resistant	26	92 (24)	NS	NS	NS	100
Turkey[31]	Izmir	2004–05	community-acquired UTI	ESBL	17	6 (1)	100	100	100	100
Turkey[23]		2006	laboratory collection	ESBL	10	20 (2)	NS	NS	NS	100
UK[15]		2001–05	bacteraemia	fluoroquinolone resistant + non-ESBL + aac(6′)-Ib-cr	10	50 (5)	NS	100	NS	0
UK[12,13]		2003–04	clinical isolates	ESBL	287	≥65 (≥188)	NS	NS	NS	100
UK[14]	north-west England	2004–05	UTI and bacteraemia	cefpodoxime resistant	88	59 (52)	NS	NS	NS	98

UK[23]		2004–07	laboratory collection	ESBL	103	81 (84)	NS	NS	NS	100
Brazil[23]		2001–05	laboratory collection	ESBL	5	0	NS	NS	NS	100
Canada[34]	Calgary	2000–07	bacteraemia	ESBL	67	31 (21)	62	100	67	100
Canada[33]		2002–04	UTI	fluoroquinolone resistant or SXT resistant	199	23 (46)	100	96	46	<2
Canada[23]		2004–06	laboratory collection	ESBL	41	41 (17)	NS	NS	NS	100
Canada[32]	Montreal	2005–07	women with UTI	varied resistance sought	353	<1 (2)	NS	NS	NS	NS
Canada[9]	Montreal	2006	women with UTI	none	256	<3	100	100	NS	NS
Canada[69]		2007	clinical isolates	ESBL	209	46 (96)	57	NS	NS	100
USA[38]	Texas	2003–05	bacteriuria in renal transplant recipients	none	40	35 (14)	NS	86	NS	0
USA[35]		2007	majority bacteraemia	varied resistance sought	127	17 (54)[a]	NS	NS	NS	56
USA[37]	Pittsburgh	2007–08	clinical isolates	ESBL	70	30 (21)	NS	NS	NS	100
USA[36]	Chicago	2008	majority UTI	ESBL	30	53 (16)	NS	100	38	100
Indian subcontinent[45]	India, Pakistan and Bangladesh	2004–06	traveller returned from region; majority UTI	ESBL	31	61 (19)	NS	NS	NS	100
Cambodia[23]	Phnom Penh	2004–05	UTI	ESBL	30	27 (8)	NS	NS	NS	100
China[42]		1998–2000	laboratory collection	fluoroquinolone resistant	12	≥17 (≥2)	NS	100	NS	NS
Japan[41]		2002–03	laboratory collection	ESBL	142	19 (27)	NS	NS	NS	100
Japan[42]		2003–07	clinical isolates	fluoroquinolone resistant	128	≥30 (≥38)	NS	100	NS	NS
Korea[43]		2006–07	community-onset UTI	fluoroquinolone resistant	129	25 (32)	100	100	50	19
Korea[42]		2005	laboratory collection	fluoroquinolone resistant	21	≥33 (≥7)	NS	100	NS	NS
Philippines[44]	Manila	2007	clinical isolates	ESBL	15	7 (1)	NS	NS	NS	100
Thailand[23]		1999	laboratory collection	ESBL	5	0	NS	NS	NS	100
Australia[48]	Queensland	2007–08	majority UTI	fluoroquinolone resistant	582	35 (205)	NS	100	NS	NS
Australia[47]	Queensland	2008–09	clinical isolates	cephalosporin resistant or fluoroquinolone resistant	49	31 (15)	NS	47	NS	53
Central African Republic[23]	Bangui	2004–06	laboratory collection	ESBL	10	50 (5)	NS	NS	NS	100

NS, not specified by the authors; UTI, urinary tract infection (or bacteriuria if not specified); ESBL, extended-spectrum β-lactamase; LTCFs, long-term care facilities; SXT, trimethoprim/sulfamethoxazole; 3GC, third-generation cephalosporin.
≥, < and > are used to estimate when the text does not give an exact number for the relevant isolate.
[a]Estimated at 17% of entire collection of *E. coli* isolates.

Europe

ST131 *E. coli* is widely disseminated amongst 'antibiotic-resistant' community and hospital-onset *E. coli* in the UK. Originally identified as the 'CTX-M ESBL-producing UK epidemic strains A–E',[12] between 2003 and 2004, these strains have subsequently been confirmed as ST131.[12,13] In one UK region, ST131 comprised 64% of community-acquired and 84% of hospital-acquired cefpodoxime-resistant *E. coli* infections.[14] A UK national study of fluoroquinolone-resistant, non-ESBL-producing *E. coli* bacteraemia isolates illustrates the rapid emergence of this strain, with isolates first identified only in 2004.[15] High rates of asymptomatic carriage of fluoroquinolone-resistant ST131 strains have been demonstrated in Northern Ireland nursing home patients.[16] In the Republic of Ireland, ST131 was also widely disseminated amongst CTX-M ESBL-producing *E. coli*.[17] No data exist on ST131 among relatively 'antibiotic-susceptible' strains.

The epidemiology of the clone throughout mainland Europe is less well characterized. Current data suggest a heterogeneous distribution of infection and carriage, with prominence of the clone amongst antibiotic-resistant isolates. A collection of fluoroquinolone-resistant *E. coli* from eight European countries showed ST131 comprised 24% of this entire group. However, the number of isolates varied markedly between countries, with Spain and Italy most prominent.[18] Spanish ESBL-producing *E. coli* data from 2004 revealed that 9% of isolates were ST131.[18] A follow-up national study in Spain in 2006 demonstrated that 13% of ESBL-producing *E. coli* were ST131 and that they had a nationwide distribution.[19,20] More recent data from a single region in Spain found that 22% of similar isolates from 2006–08 were ST131—50% originated from nursing home patients.[21] A study of a single region in Italy found that 61% of isolates selected from a collection with fluoroquinolone resistance and harbouring ESBL genes were ST131.[22] French data demonstrate the emergence of this clone primarily amongst resistant isolates. ST131 was first identified in France in 2001 and it rose to comprise 46% of ESBL-producing *E. coli* from 2006 to 2007 in one series.[23,24] Nationwide data from community-onset ESBL-producing *E. coli* infections identified that 25% were ST131, although only 1 of 40 patients was felt to have 'true community-acquired' infection.[25] Data on non-ESBL-producing *E. coli* from UTIs from 2002–03 revealed that only 3% were ST131, with the authors calculating an overall rate of 1.5% of UTIs caused by this clone.[23] Similarly, carriage of ST131 without CTX-M ESBLs has been identified in 7% of healthy volunteer stools in France.[26] In Norway, 20% of all national CTX-M-producing *E. coli* in 2003 were ST131.[27] Belgian data from 2006 to 2007 demonstrate a high prevalence of ST131 in community-acquired ESBL-producing isolates. All of the CTX-M-15-carrying *E. coli* that were assayed, comprising 62% of all isolates, were ST131.[28]

The epidemiology of other European nations can only be inferred from case reports and smaller studies. Primarily hospital-based outbreaks have been described in Croatia,[29] Portugal[11] and Germany.[30] The clone has also been identified in Austria, Germany, Hungary, Russia, Switzerland and Turkey.[10,18,31]

The Americas

The epidemiology of ST131 is well characterized in Canada, with low rates in susceptible *E. coli* and high rates in resistant isolates. Two studies comprising UTI isolates, with little antimicrobial resistance, from the years 2005–07, have demonstrated rates of ST131 in isolate collections of <3% and 1%.[9,32] In contrast, in ambulatory patient isolates selected for fluoroquinolone or trimethoprim/sulfamethoxazole resistance from 2002 to 2004, ST131 comprised 23% of all isolates and 44% of fluoroquinolone-resistant isolates.[33] Blood culture isolates of ESBL-producing *E. coli* from a single region in Canada mirror the UK experience, with emergence of the strain in 2003 and a rapid rise to comprise 41% of isolates from 2004 to 2007. An overall rise in the incidence of ESBL-producing *E. coli* bacteraemia was also attributed to the emergence of the clone.[34]

Recent data from North America suggest ST131 as 'the major cause of significantly antimicrobial-resistant *E. coli* infections in the United States'.[35] A geographically widespread selection of isolates primarily from bloodstream infections suggested that ST131 comprised 67%–69% of isolates resistant to fluoroquinolone or extended-spectrum cephalosporins. In this study, no susceptible samples were ST131.[35] Recent studies from Chicago and Pittsburgh also identified high rates amongst resistant isolates. ST131 comprised 53% of CTX-M ESBL-producing *E. coli* in Chicago and 30% of ESBL-producing *E. coli* in Pittsburgh, with a range of accompanying ESBL genes.[36,37] ST131 *E. coli* has also been identified in renal transplant recipients and haematology patients in Texas, both of which are groups with high background antimicrobial use.[38,39]

A single report has identified ST131 in South America. The clone comprised 8% of 28 ESBL-producing *E. coli* hospital-associated isolates from Rio de Janeiro, Brazil.[40]

Asia and the Middle East

ST131 has been frequently identified among antimicrobial-resistant isolates in Japan and Korea. A national survey in Japan identified the clone in 21% of ESBL-producing *E. coli* from 2002 to 2003. Interestingly, a greater genetic diversity within the clone and a greater variety of accompanying CTX-M ESBL genes was found in this region than elsewhere.[41] The clone comprised 33%–63% of fluoroquinolone-resistant isolates from various Japanese regions.[42] Amongst ciprofloxacin-resistant isolates causing community-onset infections in Korea, ST131 comprised 25% of isolates, only 19% of which harboured an ESBL gene.[43]

In a small Cambodian sample, ST131 clones comprised 27% of community-onset UTIs due to ESBL-producing *E. coli* during 2004–05.[23] Infrequent isolates have been detected among larger collections of clinical isolates in China[42] and the Philippines.[44] Faecal carriage was identified in a small number of hospital patients with ESBL-producing *E. coli* in stools in Lebanon.[10] The epidemiology in other Asian countries has been inferred from studies of returned travellers, and from the high proportion of ESBL-producing *E. coli* ST131 isolates from India, Pakistan, Iran and Lebanon.[45] Supporting these data, the SMART study showed remarkably high background rates of 79% ESBL production amongst *E. coli* isolated from intra-abdominal infections in India.[46]

Australia

Two studies from a single region of Australia recently confirmed the presence of the ST131 clone in this country. In one study of

E. coli selected for fluoroquinolone or cephalosporin resistance, 31% of isolates were ST131; <50% were CTX-M producing.[47] In a second study, 35% of fluoroquinolone-resistant isolates from a mix of hospital and community clinics were ST131.[48]

Africa

Little data exist on the presence of ST131 in Africa. Two small samples have suggested high rates amongst ESBL-producing *E. coli*. In Cape Town, South Africa, 43% of 23 such isolates were ST131 and expressed either CTX-M-14 or CTX-M-15 enzymes.[49] In the Central African Republic, 50% of CTX-M-15-producing *E. coli* were ST131.[23] A high proportion of ST131 have also been identified in a small number of travel-related ESBL-producing *E. coli* infections from Africa.[45]

Non-human carriage and infection

ST131 is represented amongst resistant isolates in companion and non-companion animals, although the extent is unclear thus far. A collection from eight European countries confirmed the presence of ST131, comprising 6% of ESBL-producing *E. coli* isolates recovered from companion animals.[50] Australian data show a surprisingly low incidence amongst fluoroquinolone-resistant isolates from companion animals (7.2% were ST131) compared with humans (35% were ST131).[48] Johnson *et al.*[51] demonstrated intrahousehold sharing of the clone between domesticated animals; however, transmission from companion animals to humans has not been confirmed.

In non-companion animals, ST131 has been identified among ESBL-producing isolates in seagulls[49] and rats,[50] both of which have close contact with human populations. Two Spanish studies have suggested a low prevalence of the clone amongst poultry and pig farms in that nation.[52,53] Mora *et al*. found that the clone comprised 1.5% of *E. coli* strains recovered from Spanish poultry between 2007 and 2009.[53] Surprisingly, in this study, the prevalence amongst *E. coli* recovered from retail chicken meat was considerably higher, comprising 7% of strains. In addition, PFGE identified a cluster of poultry and human strains, all of which carried the CTX-M-9 gene and a similar virulence profile, suggesting recent crossover between human and avian hosts.[53] The high similarity of an isolate from raw chicken and two human infections in the same geographical region in Canada was suggestive of transmission from foodstuff to humans.[32] Although these links are tantalizing, there remains to be a solid molecular epidemiological connection between human infection and prior consumption of food containing ST131 *E. coli*.

Molecular epidemiological observations

Thus far, there are 48 entries of ST131 voluntarily submitted to the largest publicly accessible *E. coli* MLST database, with isolation dates ranging from 1992 to 2009. Notably, only a handful of other STs have a greater number of entries. This may equally reflect the current interest in ST131 and/or the ubiquity of this ST amongst *E. coli*. The majority of the isolates originate from human infection, primarily UTIs. In addition, ST131 *E. coli* from domesticated and farm animals, birds and food produce are also recorded in this database.[54]

Utilizing the discriminating power of PFGE to analyse MLST-defined ST131 isolates has given considerable insight into the origin of the clone. Collections from focal outbreaks and those selected for suspected clonality have confirmed genetic similarity in excess of 85% on PGFE.[10,21] In contrast, collections with less selected samples from human or animal origin have shown ST131 isolates with considerable diversity (<65% similarity by PFGE), at times unrelated by traditional definitions. Even in such broad collections, small groups of identical or very closely related isolates are identified, often at distant locations.[13,50] This pattern likely reflects the dual phenomenon of recent divergence of the clone from a common ancestor together with ongoing transmission of the clone.[10] Clinical reports support this hypothesis. There is convincing description of direct transmission between humans[55,56] and between animals,[48] and, in contrast, of surprising diversity amongst isolates from closely associated patient groups.[38] The ancestry and significance of occasional widely divergent or unrelated ST131 isolates remains unclear.[50]

Elucidating the worldwide distribution, transmission and reservoirs of ST131 is of importance in understanding the potential mechanisms of its dissemination and control. To date, this epidemiology has not been clearly defined. Since the initial descriptions in 2008, research has focused on identifying this strain in particular groups or collections selected for antimicrobial resistance phenotype or epidemiological clustering. There have been fewer opportunities to study this strain in unselected collections of pathogenic and non-pathogenic isolates.

Reservoirs of ST131

Potential reservoirs of ST131, including food or water sources, and travel from nations with a high prevalence of the clone have been proposed as explanations for the rapid emergence of the clone on multiple continents.[57] To date, reservoirs have been detected only at a local level, with high carriage and infection rates in nursing-home residents in several nations.[16,21] Investigations have only found sporadic isolates of ST131 amongst commercial animals and food sources, although studies are limited.[32,53] The potential spread of ST131 after introduction from international travellers has only been demonstrated indirectly. Pitout *et al.*[45] found the highest proportion of ST131 clones amongst travellers with ESBL-producing infections in those returning from the Indian subcontinent and the Middle East. Freeman *et al.*[58] demonstrated a strong relationship between travel to India and community-onset CTX-M-15-producing *E. coli* infection in New Zealand. Countries implicated in these reports, such as India and Pakistan, have known high rates of ESBL-producing *E. coli* infection, but no data on the prevalence of the ST131 clone as yet.[46]

Antibiotic resistance

The ST131 'pandemic' was initially described amongst *E. coli* harbouring the CTX-M-15 ESBL gene on a relatively homogenous plasmid.[10,11] Subsequent investigation identified a high incidence of the clone amongst fluoroquinolone-resistant

non-ESBL-producing isolates and a low incidence amongst collections of susceptible *E. coli* isolates.[15,18,33,38,42] With further work, many authors have now confirmed surprising diversity amongst key transferable resistance elements, including ESBL genes, fluoroquinolone resistance genes and the plasmid scaffold harbouring them.[30,43,59] This diversity amongst a 'clonal' *E. coli* offers insight into the evolution of the clone and its resistance. Lee *et al.*[43] suggested the acquisition of transferable resistance elements as independent events from ST131 dissemination. However, the timing and sequence of resistance acquisition remains unclear. Potential explanations offered include the spread of ciprofloxacin-resistant isolates, which then acquire a CTX-M gene, or, possibly, the simultaneous spread of clonal organisms and genes.[19,42,43] Johnson *et al.*,[35] analysing North American isolates, demonstrated both vertical and horizontal transfer of the $bla_{CTX\text{-}M\text{-}15}$ gene. The gene was found in isolates closely related by PFGE; however, even within these clusters there was $bla_{CTX\text{-}M\text{-}15}$ discordance, suggesting horizontal gene transfer or, potentially, gene loss. Given the clone's propensity for the acquisition of resistance, a fine-tuning or evolutionary convergence between the clone, plasmid and acquisition of ESBL genes is likely.[11]

ESBL and AmpC enzymes

Resistance to β-lactam antibiotics in ST131 can be mediated by β-lactam-hydrolysing enzymes from three Ambler classes (A, C and D) and five distinct families. Among the ESBLs, CTX-M is the most prevalent in ST131, while SHV and TEM have been infrequently detected.[25,39,47] Of the AmpC β-lactamases, CMY has been most frequently reported.[22,37,47,60,61] Carriage of the genes encoding these β-lactamases is usually on a large plasmid (64–160 kb), which frequently carries genes encoding additional non-extended-spectrum β-lactamases, $bla_{TEM\text{-}1}$ and $bla_{OXA\text{-}1}$, and the aminoglycoside-modifying enzyme AAC(6′)-Ib-cr.[10,11,34,62]

CTX-M-15, the enzyme most closely associated with ST131, was first identified in India in 1999.[63–65] It is now the most widely distributed CTX-M worldwide.[66] The enzyme is responsible for resistance to the penicillins, cephalosporins (excluding the cephamycins) and monobactams. CTX-M takes its name from the enzyme's propensity to confer a higher level of resistance to cefotaxime than to ceftazidime (the M refers to its discovery in Munich).[67] Other CTX-M-type β-lactamases reported in association with the clone include CTX-M-2, CTX-M-3, CTX-M-9, CTX-M-14, CTX-M-27, CTX-M-32 and CTX-M-61.[23,41,53] A chromosomal rather than plasmid location of CTX-M-15 amongst ST131 isolates had also been reported and could potentially be a contributing factor in the clonal spread of CTX-M-15-producing ST131 *E. coli*.[11,22] The SHV and TEM variants described in ST131 include SHV-12, SHV-5, SHV-7, TEM-24 and TEM-116.[22,23,37,50] Isolates expressing these ESBLs may be susceptible to cefoxitin, β-lactamase inhibitors (clavulanic acid, sulbactam and tazobactam) and carbapenems. However, the co-production of ESBLs with inhibitor-resistant β-lactamases (most prominently OXA-1) renders these strains resistant to commonly used β-lactamase inhibitors like clavulanic acid. AmpC β-lactamases (such as CMY) are also resistant to β-lactamase inhibitors, as well as to cephamycins such as cefoxitin. Spanish data identified 6% of AmpC-producing *E. coli* as ST131. The remainder had mutations leading to increased expression of chromosomally located AmpC genes.[61] The range and prevalence of ESBL and AmpC genes associated with ST131 are summarized in Table 2.

Resistance to other antibiotics

Fluoroquinolone resistance is common amongst ST131 in most studies.[22,33,38] Johnson *et al.*[33,35] found that fluoroquinolone resistance and also trimethoprim/sulfamethoxazole resistance were significant markers of ST131 *E. coli* in Canada. This finding is not consistent through all regions, however.[47] The mechanism of fluoroquinolone resistance in ST131 isolates varies, depending on the level of resistance. Amongst *E. coli*, low-level fluoroquinolone resistance is usually due to a single mutation in genes encoding fluoroquinolone targets.[68] The presence of plasmid-mediated quinolone resistance genes, including *qnrA*, *qnrS* and *qnrB*, may also contribute to low-level resistance, although they are infrequently described in the ST131 clone.[34,36,43,69] Less common variations, including *qnrB1* and *qnrB2*, have also been reported associated with ST131.[22,70] The 'dual substrate' aminoglycoside-modifying enzyme AAC(6′)-Ib-cr also contributes to quinolone resistance via acetylation of selected fluoroquinolones.[71,72] The effect of these plasmid-mediated genes on fluoroquinolone MICs is greater in combination than in isolation.[72]

When present, high-level fluoroquinolone resistance in ST131 is generally due to chromosomal mutations of genes coding the fluoroquinolone targets *gyrA*, *gyrB*, *parC* and *parE*, as described in other *E. coli*.[68,73] Studies of a ciprofloxacin-resistant clone (MIC_{90} ≥32 mg/L) showed multiple mutations in *gyrA* at codons Ser-83 and Asp-87, generating Ser-83 → Leu, Asp-87 → Asn, Asp-87 → Gly or Asn-87 → Tyr amino acid changes, and further single or double mutations of *parC* at Ser-80 and/or Glu-84 codons (Ser-80 → Ile and Glu-84 → Val or Glu-84 → Gly).[22]

The aminoglycoside-modifying enzyme AAC(6′)-Ib-cr is frequently associated with ST131 (Table 2).[10,11,34,62] Other aminoglycoside resistance enzymes have been detected less frequently and sometimes in combination.[74] Resistance to aminoglycosides remains variable, despite the presence of the *aac(6′)-Ib-cr* gene. In one study where 69% of 96 ST131 *E. coli* isolates possessed this gene, 35%, 49% and 35% of isolates were resistant to gentamicin, tobramycin and amikacin, respectively.[69]

Plasmids

The initial descriptions of ST131 demonstrated the IncFII group of plasmids harbouring CTX-M-15.[11] IncFII plasmids may also encode other types of β-lactamases found in ST131 *E. coli*, including SHV-12 and CMY-2.[22,50,60] Greater clonal complexity among plasmids encoding CTX-M-15 is now apparent, with the multireplicons FIA, FIB and FII having been described in CTX-M-15-carrying plasmids of ST131 *E. coli*.[11,27,36,75] In a Norwegian study of 23 ST131 strains, the CTX-M-15 gene was related to IncFII, FIB and FIA (87%, 44% and 42%, respectively).[27]

The full sequences of two CTX-M-15-carrying plasmids of representative ST131 *E. coli* have been characterized and demonstrated extensive resistance gene profiles. The plasmid of one isolate, pEK499 (strain A: 117 536 bp), a fusion of type FII and

Table 2. ESBL, AmpC and aminoglycoside-modifying enzyme genes carried by *E. coli* ST131

Location	Number of ST131 with extended-spectrum phenotype	CTX-M-3 % (*n*)	CTX-M-14 % (*n*)	CTX-M-15 % (*n*)	Other CTX-M genes % (*n*)	Other extended-spectrum genes % (*n*)	*aac(6′)-Ib-cr* % of ST131
Multiple continents[10,11,45a]	70			99 (69)	CTX-M-1=1 (1)		100[b]
Australia[47]	8			50 (4)	untyped CTX-M=25 (2)	CMY-2=25 (2)	
Belgium[28d]	31			100 (31)			
Cambodia[23]	8		75 (6)	13 (1)	CTX-M-27=13 (1)		
Canada[23,34,69]	134		11 (15)	87 (117)	CTX-M-2=<1 (1), CTX-M-61=<1 (1)		75[b]
Central African Republic[23]	5			100 (5)			
Croatia[29]	5			100 (5)			
France[23,24]	33		21 (7)	85 (28)		TEM-24=3 (1)	
India/Pakistan/ Bangladesh[45]	19			100 (19)			
Italy[22]	11		0	91 (10)		SHV-12=9 (1)	100
Japan[41]	27		74 (20)		CTX-M-2=11 (3), CTX-M-35=15 (4)		
Korea[43]	6		17 (1)	67 (4)	CTX-M-22=17 (1)		
Norway[27]	9			89 (8)	CTX-M-1=11 (1)		
Spain[19,21,53,61,106]	82[c]		10 (8)	66 (54)	CTX-M-9=9 (7), CTX-M-10=2 (1), CTX-M-32=4 (3)	SHV-12=1 (1), CMY-2=2 (3), c-AmpC=5 (4)	100[b]
Turkey[23,31]	3	33 (1)		66 (3)			
UK[12,23]	272	19 (52)		81 (220)[d]			
USA[36,37]	37		14 (5)	78 (29)		SHV-5 or -7=8 (3)	63[b]

c-AmpC, chromosomal AmpC gene.
[a]Isolates selected for CTX-M-15 genotype by researcher.
[b]Data only available on a selection of isolates from this country.
[c]One isolate contained CTX-M-14 and CTX-M-15.
[d]Some isolates CTX-M-28.

FIA replicons, harboured resistance genes for 10 antibiotics from eight classes: $bla_{CTX\text{-}M\text{-}15}$; $bla_{OXA\text{-}1}$; $bla_{TEM\text{-}1}$; *aac(6′)-Ib-cr*; *mph*(A); *catB4*; *tet*(A); and the integron-borne *dfrA7*, *aadA5* and *sulI* genes. These were responsible for cephalosporin, β-lactamase inhibitor, aminoglycoside, chloramphenicol, tetracycline and trimethoprim/sulfamethoxazole resistance.[74]

Detection of O25b-ST131

The three major characteristics of O25b-ST131 *E. coli* are its serogroup (O25b), its phylogenetic group (B2) and its ST (ST131). Each of these characteristics has been used to aid detection. Of note, a variety of molecular techniques have been used to determine clonality in previously described clones. The ST131 'pandemic' is amongst the first examples where MLST has been the defining technique in describing a widespread bacterial strain. The power of this technique is demonstrated in several studies where reanalysis by MLST of previously defined PFGE groups has confirmed a much broader clonality than originally suspected.[13,33] This increased resolution does complicate comparison of the scope of ST131 to previous outbreaks, however.

MLST

MLST first delineated the pandemic clone and remains the 'gold standard' for identification. This requires the sequencing of pre-specified regions of highly conserved housekeeping genes, allowing comparison of nucleotide sequences with publically accessible databases. Hitherto, two separate schemas for sequencing and classification are available. Achtman *et al.*[6] defined and continue to maintain the database most frequently utilized in ST131 studies (http://mlst.ucc.ie/mlst/dbs/Ecoli).[9,10,14,37,47,76] This scheme is based on the alleles of seven housekeeping genes: *adk* (adenylate kinase); *fumC* (fumarate hydratase); *gryB* (DNA gyrase); *icd* (isocitrate dehydrogenase); *mdh* (malate dehydrogenase); *purA* (adenylosuccinate synthetase); and *recA* (ATP/GTP binding motif). An alternate *E. coli* MLST scheme also using seven housekeeping genes, operated by Michigan State University, USA (http://www.shigatox.net/ecmlst), has also been used.[34,45] All but one of the housekeeping genes used in this scheme differ from the method proposed by Achtman *et al.*[6]

PCR-based rapid detection methods

Rapid detection methods have been developed to overcome the labour intensity of MLST. Rapid detection of ST131 using a single-nucleotide polymorphism (SNP) method based on only two housekeeping genes from the Achtman MLST schema (*mdh* and *gryB*) has been developed. The O25b variants showed the SNP on C288T and C525T for *mdh*; and on C621T, C729T and T735C for *gyrB*.[33] This method has shown 100% sensitivity. When verified on a broader sample, it is likely that this method can be used as an alternative option to full MLST.

PCR-based methods to detect the phylogenetic[77] and O25 type,[76] followed by the confirmation of selected samples using MLST, have also been used.[10,27,31,38,76] This technique for detecting the O serotype O25b is based on a method originally used to type important *E. coli* causing septicaemia.[78] This O25b typing uses the specific primers rfb1bis.f (5′-ATACCGACGACGCCGATCTG-3′) and rfbO25b.r (5′-TGCTATTCATTATGCGCAGC-3′).[76] A more accurate duplex PCR-based method to detect this clone was developed by the same group. This duplex PCR-based detection method for O25b-ST131 uses allele-specific PCR for the *pabB* gene unique to phylogenetic group B2 subgroup I isolates of O type 25b.[23] The duplex PCR has been successfully used as a rapid screening method for O25b-ST131 *E. coli* in many countries.[23,36,47,79]

A PCR method on a real-time platform has recently been described. This assay utilizes amplicon melt curve analysis of two regions of the *pabB* gene. A third amplicon based on the group 1 CTX-M gene can be used to simultaneously detect the presence of $bla_{CTX\text{-}M\text{-}15}$.[80]

A third technique using triplex PCR to specifically detect CTX-M-15-producing O25b-ST131 *E. coli* is also described, based on the detection of the operon afa FM955459, *rfb*O25b and the 3′ end of $bla_{CTX\text{-}M\text{-}15}$.[21]

Repetitive sequence PCR

A semi-automated repetitive sequence-based PCR typing technique (DiversiLab®, bioMerieux) has been found to reliably identify the pandemic clone.[47,69,81,82] Although ≥95% similarity to a known ST131 strain was used to define presumed ST131 by DiversiLab in a Canadian study,[69,82] other authors have shown that ST131 strains may have similarities as low as 92%.[47,81]

PFGE

PFGE has been used to determine relationships amongst the ST131 complex, rather than to identify the clone in broader collections. The similarity of ST131 on PFGE depends on the origin of the collection. The majority of ST131 strains have similarities of ≥80% by PFGE, corresponding to differences of four to six bands.[83] However, a minority of isolates show quite a diverse PFGE pattern. For example, the similarities of ST131 *E. coli* from the UK, Chicago and Japan were only 73%,[13] 67%[36] and 70%,[41] respectively.

Virulence

E. coli ST131 is primarily an extraintestinal pathogenic *E. coli* (ExPEC) harbouring virulence genes required for successful pathogenic invasion of a human or animal host. These virulence genes allow the clone to do the following: to attach; to avoid and/or subvert host defence mechanisms within extraintestinal sites; to scavenge limiting nutrients, such as iron, from the host; and to incite a noxious host inflammatory response, cumulatively leading to extraintestinal diseases. The putative virulence genes possessed by ExPEC can be classified into at least five categories based on their function: adhesins; toxins; protectins (capsule synthesis); siderophores; and other additional virulence genes. There are 10 commonly described virulence genes in ST131 *E. coli*. They include *iha* and *fimH* (encoding the adhesin-siderophore receptor and type I fimbriae, respectively), *sat* (secreted autotransporter, a type of toxin), *kpsM* (encoding protectin II, involved in group II capsular polysaccharide synthesis), *fyuA* and *iutA* (encoding siderophores involved in synthesis and uptake of ferric yersiniabactin and aerobactin, respectively), *usp*

(uropathogenic-specific protein), *traT* (surface exclusion, serum resistance-associated), *ompT* (outer membrane protease), and *malX* (pathogenicity island marker).[10,33] The adhesins, *iha* and *fimH*, were identified in 91%–100% of O25b-ST131.[10] In addition to *iha*, Canadian O25b-ST131 *E. coli* isolates possessed the P fimbriae subunit F10 allele (98%).[33] Unlike the other typical ExPEC *E. coli*, including CGA and O15:K52:H1 *E. coli*, O25b-ST131 *E. coli* did not possess typical fimbriae and pilus tip adhesion molecules for pyelonephritis, such as those encoded by the *papA* allele, the P fimbriae structural subunit F16 allele and the *papG II* allele.[33] In Korean isolates, however, the *papG III* allele was identified in all ST131 studied.[43] The *sat* gene was present in 95%–100% of O25b-ST131 *E. coli*.[10,33] This is also a common toxin possessed by the other two types of *E. coli* (CGA and O15:K52:H1).[33] The *fyuA* and *iutA* genes, encoding the two siderophore virulence factors, were present in 95%–100% of O25b-ST131 *E. coli*.[10,33] The *kpsM II* gene was detected in 94% of O25b-ST131 CTX-M-15-producing *E. coli*.[10] In contrast, this gene appeared less frequently (54%) amongst O25b-ST131 *E. coli* in Canada that were mostly non-ESBL producers but fluoroquinolone resistant.[33] The other common *E. coli* virulence genes *usp*, *traT*, *ompT* and *malX* also appeared in nearly all ST131 *E. coli*.[10,33]

A clinical report of septic shock and emphysematous pyelonephritis, in a previously healthy individual with CTX-M-15-producing ST131, described the presence of these 10 virulence genes plus *afa* and *dra* (central region of Dr antigen-specific fimbriae, associated with binding and invasion in the mammalian urinary tract[84]).[55] These latter two virulence genes occurred in ~20% of ST131 isolates tested.[10]

The *ibeA* gene, encoding an invasion determinant associated with neonatal meningitis, has been detected in 34% of non-ESBL-producing ST131 *E. coli* blood culture isolates from north-west Spain.[53] This gene has only been infrequently reported in other collections.[33,43]

The ST131 clone has also been identified amongst adherent-invasive *E. coli* (AIEC) from intestinal and extraintestinal disease. This pathovar, distinguished from other ExPEC strains by a unique phenotype of adhesion and invasion properties, is associated with inflammatory bowel disease.[85] The intestinal AIEC phenotype ST131 carried multiple virulence genes infrequently described in the clone, including *papC*, *hlyA* and *cnf1*.[53,86]

Clermont *et al.*[76] demonstrated *in vitro* and *in vivo* virulence of the ST131 clone. Biofilm formation identified *in vitro* is a potential contributor to the long-term persistence of the clone in various environments and its resistance to host immune defences. High virulence in a 'mouse lethality' model of extraintestinal virulence was speculated to be due to unspecified virulence genes harboured by the clone.

Human infection

The spectrum of clinical infection caused by the ST131 clone appears broadly similar to that of other *E. coli*. UTI, representing the most common site of human infection with *E. coli*, is predominant. Description ranges from uncomplicated cystitis to severe infection complicated by bacteraemia, renal abscess and emphysematous pyelonephritis.[32,55] Pitout *et al.*[34] identified a propensity for urinary sepsis above other sites of infection when comparing ST131 and non-ST131 *E. coli* bacteraemia. Johnson *et al.*,[38] studying urinary tract origin isolates, found no clear correlation between ST131 and any particular clinical syndrome of renal tract infection.

Other sites of infection have included the respiratory tract, ascitic fluid, intra-abdominal abscess, bones/joints and bacteraemia without a clinically apparent focus.[41,56,87] ST131 has also been reported as a prominent cause of *E. coli* neonatal sepsis.[56] An exception to the usual spectrum of *E. coli* infection has been the description of *E. coli* ST131 pyomyositis amongst patients with haematological malignancy.[39]

Two reports illustrate direct transmission or the sharing of an identical ST131 clone between humans. Transmission of ST131 *E. coli* from an elderly father with pyelonephritis to his adult daughter after brief contact caused her to suffer a similar illness.[55] Similarly, an identical isolate was recovered from an osteoarticular infection in a young child and a faecal sample from her mother.[56]

Treatment

As mentioned above, the ST131 clone can harbour a diverse range of antimicrobial resistance mechanisms. Few descriptions of infections with the clone include details of antimicrobial therapy. Isolates harbouring CTX-M genes have been successfully treated with carbapenems alone or in combination with amikacin.[39,55] For the clinician, even with identification and susceptibilities of a pathogenic *E. coli*, the ST of the isolate is unlikely to be known. Hence, comment on therapy is based on the commonly encountered antibiotic resistance phenotypes of ST131, which would be expected to respond in a similar manner to other STs with the same antimicrobial phenotype.

Non-ESBL-producing, fluoroquinolone-resistant isolates

Fluoroquinolone resistance is a hallmark of ST131 in many series. Although not harbouring an ESBL gene, such clones frequently carry resistance to other antibiotics. Among UTI isolates, the incidence of co-resistance to trimethoprim/sulfamethoxazole was 42% in Canada,[33] 47% in Korea[43] and 70% in a European collection (including other STs).[18] Carriage of non-extended-spectrum β-lactamase enzymes confers resistance to narrow-spectrum β-lactams, with ampicillin resistance rates ranging from 90% to 94%.[18,33,43] Fortunately, almost all isolates not producing ESBLs or AmpC remain susceptible to the third-generation cephalosporins, such as ceftriaxone and cefotaxime.[38,43] In severe infection with a strain not producing ESBLs or AmpC, these would be potentially reliable treatment options. Oral therapy with an agent such as amoxicillin/clavulanate or trimethoprim/sulfamethoxazole, if susceptibility is confirmed, could also be used in less severe infection, such as uncomplicated UTI.

ESBL-producing isolates

Parenteral therapy

Using older breakpoints, ESBL-producing *E. coli* isolates may test within the susceptible MIC range to some third-generation cephalosporins. In this circumstance, many regions' laboratory

standards suggest reporting resistance to these agents due to uncertainty about their efficacy in this setting.[88] Concern arises from studies suggesting poorer outcomes with third- and fourth-generation cephalosporin therapy against ESBL producers.[89,90] Some authors suggest that β-lactam/β-lactamase inhibitor combinations may be effective where *in vitro* susceptibility of the isolate is demonstrated.[91,92] The parenteral combination piperacillin/tazobactam has been used for UTIs and other infections, including bacteraemia, skin structure infection and pneumonia, although published experience is limited.[91,92]

Amongst ST131 clones, including those not producing ESBLs, concurrent aminoglycoside resistance is frequent. Reported rates of gentamicin resistance range from 44% amongst non-ESBL-producing isolates in Korea[43] to 86% resistance in CTX-M ESBL-producing isolates.[34] Amikacin resistance is less well characterized, but also present at high rates amongst ESBL-producing isolates.[10] Even in the setting of *in vitro* susceptibility, uncertainty remains about therapeutic efficacy in severe infections, such as bloodstream infection.[93]

Carbapenems are the treatment of choice in serious ESBL-producing infection.[94] Several studies demonstrate successful therapy of UTI and non-urinary tract serious infection with meropenem or imipenem/cilastatin.[95,96] Ertapenem, a newer narrower spectrum agent, has a limited body of experience that also suggests successful therapy in ESBL-producing *E. coli* infection.[97,98] There is a report of the emergence of carbapenem resistance in *E. coli* whilst on ertapenem therapy.[99]

Tigecycline is a glycylcycline derived from minocycline with good *in vitro* activity against ESBL-producing *E. coli*.[100] There is some uncertainty about its potential drug concentrations achieved in the urinary tract.[101] However, a case report has documented successful outcomes in UTI caused by ESBL-producing *E. coli* and other highly resistant Enterobacteriaceae.[102] Temocillin, a derivative of ticarcillin with stability to β-lactamase hydrolysis and *in vitro* activity against the majority of ESBL-producing Enterobacteriaceae, is a potential therapeutic option in this setting. There is limited published experience in the treatment of a variety of ESBL-producing infections.[103]

Oral therapy

The oral combination amoxicillin/clavulanate has been used effectively in uncomplicated ESBL-producing *E. coli* cystitis when *in vitro* susceptibility is confirmed.[104] Of note, ESBL strains co-producing the non-extended-spectrum β-lactamase OXA-1 may be resistant to β-lactamase inhibitor combinations.[105]

Fosfomycin is an oral antimicrobial that inhibits cell wall biosynthesis. It has been used for the treatment of ESBL-producing *E. coli* cystitis with a high success rate.[104] Of concern, a recent report demonstrates a rapid rise in resistance rates amongst ESBL-producing ST131 clones to 22% in Spain, which is closely tied to increasing use of fosfomycin.[106]

Nitrofurantoin is a synthetic nitrofuran antimicrobial with a long history of use in uncomplicated UTI.[107] No papers directly describe the susceptibility of ST131 isolates. Amongst a European collection of fluoroquinolone-resistant non-ESBL-producing isolates, including ST131, 86% were susceptible to this agent.[18] Amongst Spanish ESBL-producing *E. coli*, 87% were susceptible.[20] It must be noted that nitrofurantoin is only useful in cystitis and not in renal infection *per se*.

Conclusions

Emerging from 'molecular obscurity' in the first decade of this century, ST131 *E. coli* is now a worldwide pathogen causing potentially severe antimicrobial-resistant infections. Disseminating in conjunction with this clone is resistance to many low-cost and easily available antimicrobials commonly used to treat *E. coli* infection. Due to the rapid evolution of this worldwide pandemic, relatively little is known about this foe.

Molecular epidemiological study is increasingly describing the clone's widespread but heterogeneous distribution amongst humans and animals. The vast majority of these data emanate from the developed world. Little is known about the distribution of ST131 in many parts of the developing world, areas suspected to have high rates of infection and which have even been postulated as reservoirs of the pathogen.[57] These areas, in addition, have a population particularly vulnerable to morbidity and mortality from resistant infection due to the limited healthcare resources available.

Two key elements required for potential control on a broader scale as a public health measure require fuller elucidation. The first is a deeper understanding of the genetics of the ST131 clone, including greater insight into why ST131 has become so finely tuned to acquire both resistance and virulence, and to rapidly disseminate on a vast scale. Research in this area should also increase our understanding of the risk of horizontal transmission of mobile resistance elements amongst ST131, between varying *E. coli* clones and, potentially, to other Enterobacteriaceae. The second element is knowledge of the dynamics of transmission and dissemination of ST131 on a population basis. We have little firm information on many of the classical descriptors of communicable disease control: reservoirs; mode of transmission; incubation period; period of communicability; susceptibility; and methods of control.[108]

Given the rapid spread of the ST131 clone and its demonstrated ability to cause severe infection in otherwise healthy individuals, consideration must be given to the planning of public health measures to attempt to control infection. A parallel could be drawn to community-associated methicillin-resistant *Staphylococcus aureus*. In order to successfully plan and execute interventions, we will need further information on key aspects of this pathogen and the dynamics of transmission.

Funding

B. A. R. receives funding via a post-graduate research scholarship from The University of Queensland.

Transparency declarations

D. L. P. has previously received research funding from Merck and AstraZeneca and has been a consultant to Merck, AstraZeneca, Johnson and Johnson, Cubist and Leo Pharmaceuticals. Both other authors: none to declare.

References

1 Mandell GL, Bennett JE, Dolin R. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. Philadelphia: Churchill Livingstone/Elsevier, 2010.

2 Hidron AI, Edwards JR, Patel J *et al*. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007. *Infect Control Hosp Epidemiol* 2008; **29**: 996–1011.

3 Gupta K, Scholes D, Stamm WE. Increasing prevalence of antimicrobial resistance among uropathogens causing acute uncomplicated cystitis in women. *JAMA* 1999; **281**: 736–8.

4 Pitout JD, Nordmann P, Laupland KB *et al*. Emergence of Enterobacteriaceae producing extended-spectrum β-lactamases (ESBLs) in the community. *J Antimicrob Chemother* 2005; **56**: 52–9.

5 Rodriguez-Bano J, Paterson DL. A change in the epidemiology of infections due to extended-spectrum β-lactamase-producing organisms. *Clin Infect Dis* 2006; **42**: 935–7.

6 Wirth T, Falush D, Lan R *et al*. Sex and virulence in *Escherichia coli*: an evolutionary perspective. *Mol Microbiol* 2006; **60**: 1136–51.

7 Manges AR, Johnson JR, Foxman B *et al*. Widespread distribution of urinary tract infections caused by a multidrug-resistant *Escherichia coli* clonal group. *N Engl J Med* 2001; **345**: 1007–13.

8 Johnson JR, Stell AL, O'Bryan TT *et al*. Global molecular epidemiology of the O15:K52:H1 extraintestinal pathogenic *Escherichia coli* clonal group: evidence of distribution beyond Europe. *J Clin Microbiol* 2002; **40**: 1913–23.

9 Manges AR, Tabor H, Tellis P *et al*. Endemic and epidemic lineages of *Escherichia coli* that cause urinary tract infections. *Emerg Infect Dis* 2008; **14**: 1575–83.

10 Nicolas-Chanoine MH, Blanco J, Leflon-Guibout V *et al*. Intercontinental emergence of *Escherichia coli* clone O25:H4-ST131 producing CTX-M-15. *J Antimicrob Chemother* 2008; **61**: 273–81.

11 Coque TM, Novais A, Carattoli A *et al*. Dissemination of clonally related *Escherichia coli* strains expressing extended-spectrum β-lactamase CTX-M-15. *Emerg Infect Dis* 2008; **14**: 195–200.

12 Woodford N, Ward ME, Kaufmann ME *et al*. Community and hospital spread of *Escherichia coli* producing CTX-M extended-spectrum β-lactamases in the UK. *J Antimicrob Chemother* 2004; **54**: 735–43.

13 Lau SH, Kaufmann ME, Livermore DM *et al*. UK epidemic *Escherichia coli* strains A–E, with CTX-M-15 β-lactamase, all belong to the international O25:H4-ST131 clone. *J Antimicrob Chemother* 2008; **62**: 1241–4.

14 Lau SH, Reddy S, Cheesbrough J *et al*. Major uropathogenic *Escherichia coli* strain isolated in the northwest of England identified by multilocus sequence typing. *J Clin Microbiol* 2008; **46**: 1076–80.

15 Jones GL, Warren RE, Skidmore SJ *et al*. Prevalence and distribution of plasmid-mediated quinolone resistance genes in clinical isolates of *Escherichia coli* lacking extended-spectrum β-lactamases. *J Antimicrob Chemother* 2008; **62**: 1245–51.

16 Dhanji H, Woodford N, Hope R *et al*. Diversity of *Escherichia coli* with CTX-M ESBLs in long-term care facilities (LTCF's) in Belfast. In: *Abstracts of the Forty-eighth Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, 2008*. Abstract C2-3890. American Society for Microbiology, Washington, DC, USA.

17 Morris D, Boyle F, Buckley V *et al*. CTX-M enzymes are the predominant extended-spectrum β-lactamases produced by Enterobacteriaceae in Ireland. *J Antimicrob Chemother* 2009; **64**: 864–6.

18 Cagnacci S, Gualco L, Debbia E *et al*. European emergence of ciprofloxacin-resistant *Escherichia coli* clonal groups O25:H4-ST 131 and O15:K52:H1 causing community-acquired uncomplicated cystitis. *J Clin Microbiol* 2008; **46**: 2605–12.

19 Oteo J, Diestra K, Juan C *et al*. Extended-spectrum β-lactamase-producing *Escherichia coli* in Spain belong to a large variety of multilocus sequence typing types, including ST10 complex/A, ST23 complex/A and ST131/B2. *Int J Antimicrob Agents* 2009; **34**: 173–6.

20 Díaz MA, Hernández-Bello JR, Rodríguez-Baño J *et al*. Diversity of *Escherichia coli* producing extended-spectrum β-lactamases in Spain: second nationwide study. *J Clin Microbiol* 2010; **48**: 2840–5.

21 Blanco M, Alonso MP, Nicolas-Chanoine MH *et al*. Molecular epidemiology of *Escherichia coli* producing extended-spectrum β-lactamases in Lugo (Spain): dissemination of clone O25b:H4-ST131 producing CTX-M-15. *J Antimicrob Chemother* 2009; **63**: 1135–41.

22 Cerquetti M, Giufre M, Garcia-Fernandez A *et al*. Ciprofloxacin-resistant, CTX-M-15-producing *Escherichia coli* ST131 clone in extraintestinal infections in Italy. *Clin Microbiol Infect* 2010; **16**: 1555–8.

23 Clermont O, Dhanji H, Upton M *et al*. Rapid detection of the O25b-ST131 clone of *Escherichia coli* encompassing the CTX-M-15-producing strains. *J Antimicrob Chemother* 2009; **64**: 274–7.

24 Courpon-Claudinon A, Lefort A, Panhard X *et al*. Bacteremia caused by third-generation cephalosporin-resistant *Escherichia coli* in France: prevalence, molecular epidemiology and clinical features. *Clin Microbiol Infect* 2010; doi:10.1111/j.1469-0691.2010.03298.x.

25 Arpin C, Quentin C, Grobost F *et al*. Nationwide survey of extended-spectrum β-lactamase-producing Enterobacteriaceae in the French community setting. *J Antimicrob Chemother* 2009; **63**: 1205–14.

26 Leflon-Guibout V, Blanco J, Amaqdouf K *et al*. Absence of CTX-M enzymes but high prevalence of clones, including clone ST131, among fecal *Escherichia coli* isolates from healthy subjects living in the area of Paris, France. *J Clin Microbiol* 2008; **46**: 3900–5.

27 Naseer U, Haldorsen B, Tofteland S *et al*. Molecular characterization of CTX-M-15-producing clinical isolates of *Escherichia coli* reveals the spread of multidrug-resistant ST131 (O25:H4) and ST964 (O102:H6) strains in Norway. *APMIS* 2009; **117**: 526–36.

28 Smet A, Martel A, Persoons D *et al*. Characterization of extended-spectrum β-lactamases produced by *Escherichia coli* isolated from hospitalized and nonhospitalized patients: emergence of CTX-M-15-producing strains causing urinary tract infections. *Microb Drug Resist* 2010; **16**: 129–34.

29 Literacka E, Bedenic B, Baraniak A *et al*. bla_{CTX-M} genes in *Escherichia coli* strains from Croatian Hospitals are located in new ($bla_{CTX-M-3a}$) and widely spread ($bla_{CTX-M-3a}$ and $bla_{CTX-M-15}$) genetic structures. *Antimicrob Agents Chemother* 2009; **53**: 1630–5.

30 Cullik A, Pfeifer Y, Prager R *et al*. A novel IS26 structure surrounds bla_{CTX-M} genes in different plasmids from German clinical *Escherichia coli* isolates. *J Med Microbiol* 2010; **59**: 580–7.

31 Yumuk Z, Afacan G, Nicolas-Chanoine MH *et al*. Turkey: a further country concerned by community-acquired *Escherichia coli* clone O25-ST131 producing CTX-M-15. *J Antimicrob Chemother* 2008; **62**: 284–8.

32 Vincent C, Boerlin P, Daignault D *et al*. Food reservoir for *Escherichia coli* causing urinary tract infections. *Emerg Infect Dis* 2010; **16**: 88–95.

33 Johnson JR, Menard M, Johnston B *et al*. Epidemic clonal groups of *Escherichia coli* as a cause of antimicrobial-resistant urinary tract infections in Canada, 2002 to 2004. *Antimicrob Agents Chemother* 2009; **53**: 2733–9.

34 Pitout JD, Gregson DB, Campbell L *et al*. Molecular characteristics of extended-spectrum-β-lactamase-producing *Escherichia coli* isolates causing bacteremia in the Calgary Health Region from 2000 to 2007: emergence of clone ST131 as a cause of community-acquired infections. *Antimicrob Agents Chemother* 2009; **53**: 2846–51.

35 Johnson JR, Johnston B, Clabots C *et al*. *Escherichia coli* sequence type ST131 as the major cause of serious multidrug-resistant *E. coli* infections in the United States. *Clin Infect Dis* 2010; **51**: 286–94.

36 Peirano G, Costello M, Pitout JD. Molecular characteristics of extended-spectrum β-lactamase-producing *Escherichia coli* from the Chicago area: high prevalence of ST131 producing CTX-M-15 in community hospitals. *Int J Antimicrob Agents* 2010; **36**: 19–23.

37 Sidjabat HE, Paterson DL, Adams-Haduch JM *et al*. Molecular epidemiology of CTX-M-producing *Escherichia coli* isolates at a tertiary medical center in western Pennsylvania. *Antimicrob Agents Chemother* 2009; **53**: 4733–9.

38 Johnson JR, Johnston B, Clabots C *et al*. *Escherichia coli* sequence type ST131 as an emerging fluoroquinolone-resistant uropathogen among renal transplant recipients. *Antimicrob Agents Chemother* 2010; **54**: 546–50.

39 Vigil KJ, Johnson JR, Johnston BD *et al*. *Escherichia coli* pyomyositis: an emerging infectious disease among patients with hematologic malignancies. *Clin Infect Dis* 2010; **50**: 374–80.

40 Peirano G, Aseni M, Pitout J. Molecular characteristics of extended-spectrum β-lactamase (ESBL) *Escherichia coli* from Rio de Janeiro, Brazil. In: *Abstracts of the Fiftieth Interscience Conference on Antimicrobial Agents and Chemotherapy, Boston, MA, 2010*. Abstract C2-680. American Society for Microbiology, Washington, DC, USA.

41 Suzuki S, Shibata N, Yamane K *et al*. Change in the prevalence of extended-spectrum-β-lactamase-producing *Escherichia coli* in Japan by clonal spread. *J Antimicrob Chemother* 2009; **63**: 72–9.

42 Uchida Y, Mochimaru T, Morokuma Y *et al*. Clonal spread in Eastern Asia of ciprofloxacin-resistant *Escherichia coli* serogroup O25 strains, and associated virulence factors. *Int J Antimicrob Agents* 2010; **35**: 444–50.

43 Lee MY, Choi HJ, Choi JY *et al*. Dissemination of ST131 and ST393 community-onset, ciprofloxacin-resistant *Escherichia coli* clones causing urinary tract infections in Korea. *J Infect* 2010; **60**: 146–53.

44 Tian GB, Garcia J, Adams-Haduch JM *et al*. CTX-M as the predominant extended-spectrum β-lactamases among Enterobacteriaceae in Manila, Philippines. *J Antimicrob Chemother* 2010; **65**: 584–6.

45 Pitout JD, Campbell L, Church DL *et al*. Molecular characteristics of travel-related extended-spectrum-β-lactamase-producing *Escherichia coli* isolates from the Calgary Health Region. *Antimicrob Agents Chemother* 2009; **53**: 2539–43.

46 Hawser SP, Bouchillon SK, Hoban DJ *et al*. Emergence of high levels of extended-spectrum-β-lactamase-producing gram-negative bacilli in the Asia-Pacific region: data from the Study for Monitoring Antimicrobial Resistance Trends (SMART) program, 2007. *Antimicrob Agents Chemother* 2009; **53**: 3280–4.

47 Sidjabat HE, Derrington P, Nimmo GR *et al*. *Escherichia coli* ST131 producing CTX-M-15 in Australia. *J Antimicrob Chemother* 2010; **65**: 1301–3.

48 Platell JL, Cobbold RN, Johnson JR *et al*. Clonal group distribution of fluoroquinolone-resistant *Escherichia coli* among humans and companion animals in Australia. *J Antimicrob Chemother* 2010; **65**: 1936–8.

49 Peirano G, Van Greune C, Pitout J. Characteristics of infections caused by extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* from community hospitals in South Africa. In: *Abstracts of the Forty-ninth Interscience Conference on Antimicrobial Agents and Chemotherapy, Boston, MA, 2010*. Abstract C2-682. American Society for Microbiology, Washington, DC, USA.

50 Ewers C, Grobbel M, Stamm I *et al*. Emergence of human pandemic O25:H4-ST131 CTX-M-15 extended-spectrum-β-lactamase-producing *Escherichia coli* among companion animals. *J Antimicrob Chemother* 2010; **65**: 651–60.

51 Johnson JR, Miller S, Johnston B *et al*. Sharing of *Escherichia coli* sequence type ST131 and other multidrug-resistant and urovirulent *E. coli* strains among dogs and cats within a household. *J Clin Microbiol* 2009; **47**: 3721–5.

52 Cortes P, Blanc V, Mora A *et al*. Isolation and characterization of potentially pathogenic antimicrobial-resistant *Escherichia coli* strains from chicken and pig farms in Spain. *Appl Environ Microbiol* 2010; **76**: 2799–805.

53 Mora A, Herrera A, Mamani R *et al*. Recent emergence of clonal group O25b:K1:H4-B2-ST131 *ibeA* among *Escherichia coli* isolated from poultry, including CTX-M-9-producing strains. Comparison with clinical human strains. *Appl Environ Microbiol* 2010; doi:10.1128/AEM.01112–10.

54 University College Cork I. MLST Databases at ERI, University College Cork. *Escherichia coli* MLST Database. http://mlst.ucc.ie/mlst/dbs/Ecoli (30 March 2010, date last accessed).

55 Ender PT, Gajanana D, Johnston B *et al*. Transmission of an extended-spectrum-β-lactamase-producing *Escherichia coli* (sequence type ST131) strain between a father and daughter resulting in septic shock and emphysematous pyelonephritis. *J Clin Microbiol* 2009; **47**: 3780–2.

56 Johnson JR, Anderson JT, Clabots C *et al*. Within-household sharing of a fluoroquinolone-resistant *Escherichia coli* sequence type ST131 strain causing pediatric osteoarticular infection. *Pediatr Infect Dis J* 2010; **29**: 473–5.

57 Pitout JD. Infections with extended-spectrum β-lactamase-producing Enterobacteriaceae: changing epidemiology and drug treatment choices. *Drugs* 2010; **70**: 313–33.

58 Freeman JT, McBride SJ, Heffernan H *et al*. Community-onset genitourinary tract infection due to CTX-M-15-producing *Escherichia coli* among travelers to the Indian subcontinent in New Zealand. *Clin Infect Dis* 2008; **47**: 689–92.

59 Carattoli A, Garcia-Fernandez A, Varesi P *et al*. Molecular epidemiology of *Escherichia coli* producing extended-spectrum β-lactamases isolated in Rome, Italy. *J Clin Microbiol* 2008; **46**: 103–8.

60 Naseer U, Haldorsen B, Simonsen GS *et al*. Sporadic occurrence of CMY-2-producing multidrug-resistant *Escherichia coli* of ST-complexes 38 and 448, and ST131 in Norway. *Clin Microbiol Infect* 2010; **16**: 171–8.

61 Oteo J, Cercenado E, Cuevas O *et al*. AmpC β-lactamases in *Escherichia coli*: emergence of CMY-2-producing virulent phylogroup D isolates belonging mainly to STs 57, 115, 354, 393, and 420, and phylogroup B2 isolates belonging to the international clone O25b-ST131. *Diagn Microbiol Infect Dis* 2010; **67**: 270–6.

62 Boyd DA, Tyler S, Christianson S *et al*. Complete nucleotide sequence of a 92-kilobase plasmid harboring the CTX-M-15 extended-spectrum β-lactamase involved in an outbreak in long-term-care facilities in Toronto, Canada. *Antimicrob Agents Chemother* 2004; **48**: 3758–64.

63 Olson AB, Silverman M, Boyd DA *et al*. Identification of a progenitor of the CTX-M-9 group of extended-spectrum β-lactamases from *Kluyvera georgiana* isolated in Guyana. *Antimicrob Agents Chemother* 2005; **49**: 2112–5.

64 Poirel L, Kampfer P, Nordmann P. Chromosome-encoded Ambler class A β-lactamase of *Kluyvera georgiana*, a probable progenitor of a subgroup of CTX-M extended-spectrum β-lactamases. *Antimicrob Agents Chemother* 2002; **46**: 4038–40.

65 Karim A, Poirel L, Nagarajan S *et al*. Plasmid-mediated extended-spectrum β-lactamase (CTX-M-3 like) from India and gene association with insertion sequence ISEcp1. *FEMS Microbiol Lett* 2001; **201**: 237–41.

66 Canton R, Coque TM. The CTX-M β-lactamase pandemic. *Curr Opin Microbiol* 2006; **9**: 466–75.

67 Bauernfeind A, Grimm H, Schweighart S. A new plasmidic cefotaximase in a clinical isolate of *Escherichia coli*. *Infection* 1990; **18**: 294–8.

68 Vila J, Ruiz J, Marco F *et al*. Association between double mutation in *gyrA* gene of ciprofloxacin-resistant clinical isolates of *Escherichia coli* and MICs. *Antimicrob Agents Chemother* 1994; **38**: 2477–9.

69 Peirano G, Richardson D, Nigrin J *et al*. High prevalence of ST131 isolates producing CTX-M-15 and CTX-M-14 among extended-spectrum-β-lactamase-producing *Escherichia coli* isolates from Canada. *Antimicrob Agents Chemother* 2010; **54**: 1327–30.

70 Pomba C, da Fonseca JD, Baptista BC *et al*. Detection of the pandemic O25-ST131 human virulent *Escherichia coli* CTX-M-15-producing clone harboring the *qnrB2* and *aac(6′)-Ib-cr* genes in a dog. *Antimicrob Agents Chemother* 2009; **53**: 327–8.

71 Robicsek A, Jacoby GA, Hooper DC. The worldwide emergence of plasmid-mediated quinolone resistance. *Lancet Infect Dis* 2006; **6**: 629–40.

72 Robicsek A, Strahilevitz J, Jacoby GA *et al*. Fluoroquinolone-modifying enzyme: a new adaptation of a common aminoglycoside acetyltransferase. *Nat Med* 2006; **12**: 83–8.

73 Ruiz J, Marco F, Goni P *et al*. High frequency of mutations at codon 83 of the *gyrA* gene of quinolone-resistant clinical isolates of *Escherichia coli*. *J Antimicrob Chemother* 1995; **36**: 737–8.

74 Woodford N, Carattoli A, Karisik E *et al*. Complete nucleotide sequences of plasmids pEK204, pEK499, and pEK516, encoding CTX-M enzymes in three major *Escherichia coli* lineages from the United Kingdom, all belonging to the international O25:H4-ST131 clone. *Antimicrob Agents Chemother* 2009; **53**: 4472–82.

75 Montesinos I, Rodriguez-Villalobos H, De Mendonça R *et al*. Molecular characterization of plasmids encoding CTX-M-15 extended-spectrum β-lactamase associated with the ST131 *Escherichia coli* clone in Belgium. *J Antimicrob Chemother* 2010; **65**: 1828–30.

76 Clermont O, Lavollay M, Vimont S *et al*. The CTX-M-15-producing *Escherichia coli* diffusing clone belongs to a highly virulent B2 phylogenetic subgroup. *J Antimicrob Chemother* 2008; **61**: 1024–8.

77 Clermont O, Bonacorsi S, Bingen E. Rapid and simple determination of the *Escherichia coli* phylogenetic group. *Appl Environ Microbiol* 2000; **66**: 4555–8.

78 Clermont O, Johnson JR, Menard M *et al*. Determination of *Escherichia coli* O types by allele-specific polymerase chain reaction: application to the O types involved in human septicemia. *Diagn Microbiol Infect Dis* 2007; **57**: 129–36.

79 Severin JA, Mertaniasih NM, Kuntaman K *et al*. Molecular characterization of extended-spectrum β-lactamases in clinical *Escherichia coli* and *Klebsiella pneumoniae* isolates from Surabaya, Indonesia. *J Antimicrob Chemother* 2010; **65**: 465–9.

80 Dhanji H, Doumith M, Clermont O *et al*. Real-time PCR for detection of the O25b-ST131 clone of *Escherichia coli* and its CTX-M-15-like extended-spectrum β-lactamases. *Int J Antimicrob Agents* 2010; **36**: 355–8.

81 Lau SH, Cheesborough J, Kaufmann ME *et al*. Rapid identification of uropathogenic *Escherichia coli* of the O25:H4-ST131 clonal lineage using the DiversiLab repetitive sequence-based PCR system. *Clin Microbiol Infect* 2010; **16**: 232–7.

82 Pitout JD, Campbell L, Church DL *et al*. Using a commercial DiversiLab semiautomated repetitive sequence-based PCR typing technique for identification of *Escherichia coli* clone ST131 producing CTX-M-15. *J Clin Microbiol* 2009; **47**: 1212–5.

83 Tenover FC, Arbeit RD, Goering RV *et al*. Interpreting chromosomal DNA restriction patterns produced by pulsed-field gel electrophoresis: criteria for bacterial strain typing. *J Clin Microbiol* 1995; **33**: 2233–9.

84 Johnson JR. Virulence factors in *Escherichia coli* urinary tract infection. *Clin Microbiol Rev* 1991; **4**: 80–128.

85 Boudeau J, Glasser AL, Masseret E *et al*. Invasive ability of an *Escherichia coli* strain isolated from the ileal mucosa of a patient with Crohn's disease. *Infect Immun* 1999; **67**: 4499–509.

86 Martinez-Medina M, Mora A, Blanco M *et al*. Similarity and divergence among adherent-invasive *Escherichia coli* and extraintestinal pathogenic *E. coli* strains. *J Clin Microbiol* 2009; **47**: 3968–79.

87 Bert F, Johnson JR, Ouattara B *et al*. Genetic diversity and virulence profiles of *Escherichia coli* isolates causing spontaneous bacterial peritonitis and bacteremia in patients with cirrhosis. *J Clin Microbiol* 2010; **48**: 2709–14.

88 Livermore DM, Brown DFJ. Detection of β-lactamase-mediated resistance. *J Antimicrob Chemother* 2001; **48** Suppl 1: 59–64.

89 Du B, Long Y, Liu H *et al*. Extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* bloodstream infection: risk factors and clinical outcome. *Intensive Care Med* 2002; **28**: 1718–23.

90 Zanetti G, Bally F, Greub G *et al*. Cefepime versus imipenem–cilastatin for treatment of nosocomial pneumonia in intensive care unit patients: a multicenter, evaluator-blind, prospective, randomized study. *Antimicrob Agents Chemother* 2003; **47**: 3442–7.

91 Tumbarello M, Spanu T, Sanguinetti M *et al*. Bloodstream infections caused by extended-spectrum-β-lactamase-producing *Klebsiella pneumoniae*: risk factors, molecular epidemiology, and clinical outcome. *Antimicrob Agents Chemother* 2006; **50**: 498–504.

92 Gavin PJ, Suseno MT, Thomson RB Jr *et al*. Clinical correlation of the CLSI susceptibility breakpoint for piperacillin–tazobactam against extended-spectrum-β-lactamase-producing *Escherichia coli* and *Klebsiella species*. *Antimicrob Agents Chemother* 2006; **50**: 2244–7.

93 Kim YK, Pai H, Lee HJ *et al*. Bloodstream infections by extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in children: epidemiology and clinical outcome. *Antimicrob Agents Chemother* 2002; **46**: 1481–91.

94 Paterson DL. Recommendation for treatment of severe infections caused by Enterobacteriaceae producing extended-spectrum β-lactamases (ESBLs). *Clin Microbiol Infect* 2000; **6**: 460–3.

95 Kang CI, Kim SH, Park WB *et al*. Bloodstream infections due to extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*: risk factors for mortality and treatment outcome, with special emphasis on antimicrobial therapy. *Antimicrob Agents Chemother* 2004; **48**: 4574–81.

96 Paterson DL, Ko WC, Von Gottberg A *et al*. Antibiotic therapy for *Klebsiella pneumoniae* bacteremia: implications of production of extended-spectrum β-lactamases. *Clin Infect Dis* 2004; **39**: 31–7.

97 Bassetti M, Righi E, Fasce R *et al*. Efficacy of ertapenem in the treatment of early ventilator-associated pneumonia caused by extended-spectrum β-lactamase-producing organisms in an intensive care unit. *J Antimicrob Chemother* 2007; **60**: 433–5.

98 Lye DC, Wijaya L, Chan J *et al*. Ertapenem for treatment of extended-spectrum β-lactamase-producing and multidrug-resistant gram-negative bacteraemia. *Ann Acad Med Singapore* 2008; **37**: 831–4.

99 Oteo J, Delgado-Iribarren A, Vega D *et al*. Emergence of imipenem resistance in clinical *Escherichia coli* during therapy. *Int J Antimicrob Agents* 2008; **32**: 534–7.

100 Morosini MI, Garcia-Castillo M, Coque TM *et al*. Antibiotic coresistance in extended-spectrum-β-lactamase-producing Enterobacteriaceae and

in vitro activity of tigecycline. *Antimicrob Agents Chemother* 2006; **50**: 2695–9.

101 Nix DE, Matthias KR. Should tigecycline be considered for urinary tract infections? A pharmacokinetic re-evaluation. *J Antimicrob Chemother* 2010; **65**: 1311–2.

102 Tsioutis C, Kritsotakis EI, Maraki S *et al*. Infections by pandrug-resistant gram-negative bacteria: clinical profile, therapeutic management, and outcome in a series of 21 patients. *Eur J Clin Microbiol Infect Dis* 2010; **29**: 301–5.

103 Frankard J, Byl B, Rodriguez-Villalobos H *et al*. Clinical presentation and outcomes of multi-resistant *Enterobacter aerogenes* infections: a review of 116 episodes. *Clin Microbiol Infect* 2004; **10**: 366–485.

104 Rodriguez-Bano J, Alcala JC, Cisneros JM *et al*. Community infections caused by extended-spectrum β-lactamase-producing *Escherichia coli*. *Arch Intern Med* 2008; **168**: 1897–902.

105 Livermore DM, Hope R, Mushtaq S *et al*. Orthodox and unorthodox clavulanate combinations against extended-spectrum β-lactamase producers. *Clin Microbiol Infect* 2008; **14** Suppl 1: 189–93.

106 Oteo J, Orden B, Bautista V *et al*. CTX-M-15-producing urinary *Escherichia coli* O25b-ST131-phylogroup B2 has acquired resistance to fosfomycin. *J Antimicrob Chemother* 2009; **64**: 712–7.

107 Garau J. Other antimicrobials of interest in the era of extended-spectrum β-lactamases: fosfomycin, nitrofurantoin and tigecycline. *Clin Microbiol Infect* 2008; **14** Suppl 1: 198–202.

108 Heymann DL. *American Public Health Association. Control of Communicable Diseases Manual*. Washington, DC: American Public Health Association, 2008.

109 Rooney PJ, O'Leary MC, Loughrey AC *et al*. Nursing homes as a reservoir of extended-spectrum β-lactamase (ESBL)-producing ciprofloxacin-resistant *Escherichia coli*. *J Antimicrob Chemother* 2009; **64**: 635–41.