*J Antimicrob Chemother* 2021; **76**: 2745–2747
doi:10.1093/jac/dkab251 Advance Access publication 23 July 2021

Journal of Antimicrobial Chemotherapy

# Rise in the prevalence of resistance to extended-spectrum cephalosporins in the USA, nursing homes and antibiotic prescribing in outpatient and inpatient settings

**Edward Goldstein[1]***

[1]*Center for Communicable Disease Dynamics, Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, USA*

*E-mail: egoldste@hsph.harvard.edu

The prevalence of resistance to extended-spectrum (ES) cephalosporins for multiple types of infections treated in US hospitals and the incidence of hospitalization with ESBL-producing Enterobacteriaceae (many of which are detected in nursing home residents) have grown markedly in recent years. Here, I review these developments, as well as evidence for their adverse consequences, including the increase in the overall burden of bacterial infections due to proliferation of ESBL-producing/ES cephalosporin-resistant bacteria, the contribution of ESBL-producing/ES cephalosporin-resistant bacteria to the increase in the burden of mortality associated with bacterial infections and the contribution of the proliferation of ESBL-producing bacteria to the prevalence of carbapenem resistance. I argue that in order to mitigate the escalation of these phenomena, a reduction in outpatient prescribing of cephalosporins, especially to older adults, mitigation of transmission of ESBL-producing organisms in nursing homes and a reduction in inpatient prescribing of ES cephalosporins (which has seen a major increase in recent years) are needed.

Pronounced growth in the prevalence of resistance to extended-spectrum (ES) cephalosporins in invasive *Escherichia coli* infections in hospitalized patients in the US has recently been documented,[1] with prevalence of resistance increasing from 5.46% to 12.97% between 2009 and 2017. A study of device- and procedure-related *E. coli* infections in US hospitals between 2013 and 2017 also found a significant increase in the prevalence of resistance to ES cephalosporins.[2] Many of the bacteria resistant to ES cephalosporins are ESBL-producing organisms that are challenging to treat, with ESBL-producing Enterobacteriaceae being listed among serious threats related to antimicrobial resistance by the US CDC.[3] The incidence of ESBL-producing Enterobacteriaceae in hospitalized patients in the US has increased by 53.3% between 2012 and 2017, while the incidence of other important resistance phenotypes, such as VRE, MRSA and MDR *Pseudomonas aeruginosa*, declined during the same period.[4] Another study involving 411 US hospitals found a similar increase in the rate of ESBL-producing Enterobacteriaceae detection in hospitalized patients between 2013 and 2017.[5] Proliferation of ESBL-producing Enterobacteriaceae leads to several adverse effects.

### *(i) Increase in the burden of infections and related adverse outcomes due to recurrence of infection*

Resistance to ES cephalosporins/ESBL phenotype is a risk factor for recurrent infections. For example, ES cephalosporin resistance in urinary tract infections (UTIs) with Enterobacteriaceae was found to be a hazard of a recurrent UTI[6] and resistance to third-generation cephalosporins in Enterobacteriaceae-associated bacteraemia was found to carry the risk of a recurrent bacteraemia.[7]

### *(ii) Increase in the burden of severe infections due to progression to severe infections for ESBL-producing bacterial infections not cleared by antibiotic treatment*

A study of 502 adult inpatients admitted to a hospital system in Utah, USA with a community-acquired UTI estimated that prior antibiotic exposure (within a 3 month period preceding the index hospitalization) is a very significant risk factor for the carriage of the ESBL phenotype.[8] It is likely that in many instances of hospitalization following antibiotic treatment, ESBL infections resulting in hospitalizations were not cleared by prior antibiotic treatment of an earlier ESBL infection, rather than emerging as *de novo* ESBL infections following prior antibiotic treatment and leading to hospitalization, particularly for the more recent prior infections treated with antibiotics.

### *(iii) Contribution of ESBL phenotypes to the increase in the burden of mortality*

As noted above, ESBL phenotypes/bacteria resistant to ES cephalosporins boost the volume of infections in both the inpatient and the outpatient settings, thus increasing the volume of mortality

from bacterial infections. There are additional ways in which ESBL phenotypes/bacteria resistant to ES cephalosporins increase the volume of mortality from bacterial infections. Several studies found that underlying health conditions, such as cerebrovascular disease and diabetes mellitus, are risk factors for the carriage of ESBL- versus non-ESBL-producing Enterobacteriaceae in different types of infection (possibly due to differences in prior antibiotic exposure and other factors).[9,10] Additionally, some studies found that resistance to ES cephalosporins is an independent risk factor for mortality for *E. coli* and *Klebsiella pneumoniae* infections,[11] whereas other studies found no such additional independent risks.[12,13] Altogether, mortality rates for patients with ESBL-producing *E. coli* and *K. pneumoniae* infections are higher than for patients with non-ESBL infections—even if ESBL phenotype is not an independent risk factor for mortality in bloodstream infections when adjusted for other risk factors, patients with ESBL-producing infections have a higher prevalence of underlying health conditions compared with patients with non-ESBL infections,[9,10] with those underlying health conditions being risk factors for mortality in bloodstream infections.[12]

### *(iv) Contribution of ESBL phenotypes to the increase in the prevalence of carbapenem resistance*

Carbapenem antibiotics are the drug of choice for treating ESBL-producing bacteria.[14] Additionally, a combination of ESBL and/or AmpC production and alterations of porin synthesis is one of the mechanisms that leads to carbapenem resistance.[15,16] Altogether, the rise in the prevalence of ESBL phenotypes contributes to carbapenem use and to the proliferation of carbapenem resistance.

A study of ESBL-producing *E. coli* and *K. pneumoniae* infections in hospitalized patients in the southeastern USA found that most of those infections were healthcare associated (nursing home residents, patients hospitalized within 12 months of admission and certain other categories).[17] A study of ESBL-producing *E. coli* and *K. pneumoniae* infections in hospitalized patients in North Carolina found that just over half of those patients were nursing home residents.[18] A study of *E. coli*-associated bacteriuria in Minnesota found that rates of infections resistant to ES cephalosporins are much higher in persons aged 65–79 years and over 80 years compared with persons aged 18–64 years.[19] This suggests that in order to mitigate the proliferation of ESBL-producing/ES cephalosporin-resistant infections, a reduction in outpatient prescribing of cephalosporins to older adults (including unnecessary prescribing for respiratory infections) and mitigation of transmission of ESBL-producing organisms in nursing homes are needed. In particular, infection prevention (IP) training in nursing home staff contributes to better antibiotic stewardship practices in nursing homes,[20] whereas antibiotic stewardship programmes in hospitals improve prescribing and microbial outcomes.[21] For some studies,[17,19] a sizeable proportion of ESBL-producing/ES cephalosporin-resistant infections were community-onset infections and were not healthcare associated. This, together with the prominent role of outpatient antibiotic prescribing in promoting antimicrobial resistance,[22] suggests that a reduction in outpatient prescribing of cephalosporins to non-elderly individuals, both through antibiotic replacement and a reduction in unnecessary prescribing, particularly for respiratory causes, should also be beneficial for stemming the spread of ESBL-producing/ES cephalosporin-resistant infections in the USA. Additionally, there is an ongoing shift from broad-spectrum to narrow-spectrum antibiotics in the outpatient setting in the USA[23] and it should also help to mitigate the proliferation of resistance to ES cephalosporins. Finally, prescribing of ES cephalosporins in US hospitals increased significantly in recent years (by 32% between 2012 and 2017).[24] This, together with the relatively high frequency of prior hospitalization for ESBL-colonized residents in nursing homes reported in some studies,[25] suggests the benefits of a reduction in inpatient prescribing of ES cephalosporins in the USA, particularly to older individuals.

## Funding

This work was supported by the Wellcome Trust (Award # 219759/Z/19/Z) and by Award Number U54GM088558 from the National Institute of General Medical Sciences.

## Transparency declarations

None to declare.

## References

**1** Begier E, Rosenthal NA, Gurtman A *et al.* Epidemiology of invasive *Escherichia coli* infection and antibiotic resistance status among patients treated in U.S. hospitals: 2009–2016. *Clin Infect Dis* 2021; doi:10.1093/cid/ciab005.

**2** Kourtis AP, Sheriff EA, Weiner-Lastinger LV *et al.* Antibiotic multidrug resistance of *Escherichia coli* causing device- and procedure-related infections in the United States reported to the National Healthcare Safety Network, 2013–2017. *Clin Infect Dis* 2020; doi:10.1093/ciaa1031.

**3** US CDC. Antibiotic Resistance Threats in the United States. 2019. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf.

**4** Jernigan JA, Hatfield KM, Wolford H *et al.* Multidrug-resistant bacterial infections in U.S. hospitalized patients, 2012–2017. *N Engl J Med* 2020; **382**: 1309–19.

**5** Gupta V, Ye G, Olesky M *et al.* Trends in resistant Enterobacteriaceae and *Acinetobacter* species in hospitalized patients in the United States: 2013–2017. *BMC Infect Dis* 2019; **19**: 742.

**6** Anesi JA, Lautenbach E, Nachamkin I *et al.* The role of extended-spectrum cephalosporin-resistance in recurrent community-onset Enterobacteriaceae urinary tract infections: a retrospective cohort study. *BMC Infect Dis* 2019; **19**: 163.

**7** Woudt SHS, de Greeff SC, Schoffelen AF *et al.* Antibiotic resistance and the risk of recurrent bacteremia. *Clin Infect Dis* 2018; **66**: 1651–7.

**8** Goyal D, Dean N, Neill S *et al.* Risk factors for community-acquired extended-spectrum β-lactamase–producing Enterobacteriaceae infections—a retrospective study of symptomatic urinary tract infections. *Open Forum Infect Dis* 2019; **6**: ofy357.

**9** Søraas A, Sundsfjord A, Sandven I *et al.* Risk factors for community-acquired urinary tract infections caused by ESBL-producing Enterobacteriaceae—a case–control study in a low prevalence country. *PLoS One* 2013; **8**: e69581.

**10** Nakai H, Hagihara M, Kato H *et al.* Prevalence and risk factors of infections caused by extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae. *J Infect Chemother* 2016; **22**: 319–26.

**11** Mark DG, Hung Y-Y, Salim Z *et al*. Third-generation cephalosporin resistance and associated discordant antibiotic treatment in emergency department febrile urinary tract infections. *Ann Emerg Med* 2021; doi: 10.1016/j.annemergmed.2021.01.003.

**12** Gürntke S, Kohler C, Steinmetz I *et al*. Molecular epidemiology of extended-spectrum β-lactamase (ESBL)-positive *Klebsiella pneumoniae* from bloodstream infections and risk factors for mortality. *J Infect Chemother* 2014; **20**: 817–9.

**13** Denis B, Lafaurie M, Donay J-L *et al*. Prevalence, risk factors, and impact on clinical outcome of extended-spectrum β-lactamase-producing *Escherichia coli* bacteraemia: a five-year study. *Int J Infect Dis* 2015; **39**: 1–6.

**14** Rodríguez-Baño J, Gutiérrez-Gutiérrez B, Machuca I *et al*. Treatment of infections caused by extended-spectrum-β-lactamase-, AmpC-, and carbapenemase-producing Enterobacteriaceae. *Clin Microbiol Rev* 2018; **31**: e00079-17.

**15** Codjoe FS, Donko ES. Carbapenem resistance: a review. *Med Sci (Basel)* 2018; **6**: 1.

**16** Nicolas-Chanoine H-M, Vigan M, Laouénan C *et al*. Risk factors for carbapenem-resistant Enterobacteriaceae infections: a French case-control-control study. *Eur J Clin Microbiol Infect Dis* 2019; **38**: 383–93.

**17** Thaden JT, Fowler VG, Sexton DJ *et al*. Increasing incidence of extended-spectrum β-lactamase-producing *Escherichia coli* in community hospitals throughout the southeastern United States. *Infect Control Hosp Epidemiol* 2016; **37**: 49–54.

**18** Freeman JT, Sexton DJ, Anderson DJ. Emergence of extended-spectrum β-lactamase-producing *Escherichia coli* in community hospitals throughout North Carolina: a harbinger of a wider problem in the United States? *Clin Infect Dis* 2009; **49**: e30–2.

**19** Swami SK, Liesinger JT, Shah N *et al*. Incidence of antibiotic-resistant *Escherichia coli* bacteriuria according to age and location of onset: a population-based study from Olmsted County, Minnesota. *Mayo Clin Proc* 2012; **87**: 753–9.

**20** Stone PW, Herzig CTA, Agarwal M *et al*. Nursing home infection control program characteristics, CMS citations, and implementation of antibiotic stewardship policies: a national study. *Inquiry* 2018; **55**: 0046958018778636.

**21** Wagner B, Filice GA, Drekonja D *et al*. Antimicrobial stewardship programs in inpatient hospital settings: a systematic review. *Infect Control Hosp Epidemiol* 2014; **35**: 1209–28.

**22** MacFadden DR, Fisman DN, Hanage WP *et al*. The relative impact of community and hospital antibiotic use on the selection of extended-spectrum β-lactamase-producing *Escherichia coli*. *Clin Infect Dis* 2019; **69**: 182–8.

**23** King LM, Bartoces M, Fleming-Dutra KE *et al*. Changes in US outpatient antibiotic prescriptions from 2011–2016. *Clin Infect Dis* 2020; **70**: 370–7.

**24** Baggs J, Kazakova S, Hatfield KM *et al*. Trends in inpatient antibiotic use in US hospitals, 2012–2017. *Open Forum Infect Dis* 2019; **6** Suppl 2: S79.

**25** 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.