Antibiotics: challenges and opportunities

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Professor Matteo Bassetti
Head Infectious Diseases Division
Department of Specialist Medicine
Santa Maria della Misericordia di Udine
Genova, Italy

Paula Hensler
Independent Medical Writer
London, UK

Abstract

The European Congress of Clinical Microbiology and Infectious Diseases, the annual meeting of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) is the most attended infectious disease conference worldwide. This year, more than 10,000 clinicians and scientists attended the congress to present and share the latest research breakthrough in infectious diseases. This article reviews the sessions that addressed the challenges of the increasing antibiotic resistance, antibiotic stewardship and the responsible use of antibiotics.

Key words: antibiotics, infectious diseases, antibiotic resistance, antibiotic stewardship, Gram positive, Gram negative, carbapenemases, MRSA

Antimicrobial susceptibility

EUCAST (European Committee on Antimicrobial Susceptibility Testing) provides common European breakpoints and antimicrobial susceptibility testing methodology under the administrative, scientific, and financial support of ECCMID. Speaking at ECCMID 2015, Rafael Canton Moreno (Madrid, Spain) presented an update on the EUCAST methods and breakpoints in view of the publication of version 5.0 of the EUCAST breakpoint and EUCAST QC-tables on the EUCAST website in January 2015. Financial support was provided from the European Centre for Disease Prevention and Control (ECDC) (Moreno 2015).

Moreno described the new breakpoints as part of the marketing authorisation process by the European Medicines Agency (EMA), including those for dalbavancin. He also discussed the harmonised nitroxoline and temocillin breakpoints for Enterobacteriaceae and sulbactam breakpoints for *Acintetobacter* spp., which will require new information for final decisions. Linezolid breakpoints for staphylococci and enterococci, metronidazole

breakpoints for anaerobes, fluoroquinolone breakpoints for *Corynebacterium* spp. and teicoplanin breakpoints for coagulase-negative staphylococci have also been reviewed. Moreno explained that the breakpoint changes considered could not be justified. The methodology used for telavancin MICs determination was revised and breakpoints adjusted in line with changes in MIC distributions, added Moreno. The methodology for colistin broth microdilution in conjunction with CLSI was also decided at this time.

Moreno informed the audience that for *Neisseria meningitidis*, a proposal to remove the intermediate category for ciprofloxacin was agreed after wide consultation.

Breakpoints currently being reviewed include carbapenems and tigecycline for Enterobacteriaceae and fluoroquinolone for different organisms. A guidance note on breakpoints for topical agents was also published; the development of rationale documents continues and that for ceftobiprole has been released. Moreno explained that EUCAST has the objective to develop guidelines for companies submitting new antimycobacterial agents, in collaboration with the ESCMID study group for Mycobacterial Infections (ESGMYC) and EMA, following previous experience in setting breakpoints for delamanid and bedaqualine and *Mycobacterium tuberculosis*.

Community-acquired MRSA

Community-acquired (CA) methicillin-resistant *Staphylococcus aureus* (MRSA) remains at the forefront of challenges faced by the infectious diseases specialists and clinicians worldwide.

Speaking during ECCMID 2015, Robert L Skov (Copenhagen, Denmark) discussed the definition of CA-MRSA, hospital-associated MRSA (HA-MRSA), and livestock-associated MRSA (LA-MRSA) - the three major types of MRSA (Skov 2015). He explained that while for about 30 years MRSA was closely associated with hospitalisation, in the late 1990s, MRSA infections were increasingly seen in patients with no recent contact with the healthcare system. These CA-MRSA infections were caused by a number of strains distinct from the HA-MRSA strain types. Skov described the 5 “Cs” of this type of CA-MRSA infection: **C**rowding, **C**ontaminated surfaces and shared items, Frequent skin **C**ontact, Poor hygiene/**C**leanliness, and **C**ompromised skin; these are different from the traditional risk factors such as previous hospitalisation, central lines or surgical procedure(s). He added that CA-MRSA strains most often carry the *mecA* gene in the smaller cassettes (*SCCmec* IV and V) compared to the larger *SCCmec* II and III found in HA-MRSA. CA-MRSA is most often PVL positive and typically causes skin and soft tissue infections (SSTIs) often in children and younger adults. However, when introduced into the healthcare setting they may cause severe infections including surgical site infections and bacteraemia.

Skov discussed how a new reservoir for MRSA has emerged in production animals (LA-MRSA), which has expanded explosively and worldwide. In Europe, the CC398 strain is the most abundant with pigs being the main reservoir for MRSA CC398. It also is found in veal calves, poultry and in horses. Microbiologically, these strains differ not only in being of distinct ST types but also in carrying distinct SCC*mec cassettes* (like 5C2&5) and displaying the loss of the Sa3 phage. Skov mentioned that whereas HA-MRSA is declining in many European countries, the prevalence of CA-MRSA and LA-MRSA is increasing. This may increase the general prevalence of MRSA carriage thus ultimately threatening control of MRSA in hospitals and other healthcare settings.

The ECCMID audience heard from Ulrich Nuebel (Braunschweig, Germany) on how recent population-scale genomic analyses provided unprecedented insights into CA-MRSA epidemiology and biology (Nuebel 2015). Based on multiple genome sequences from each of major CA-MRSA clones, the spatial and temporal dynamics of their spread has been reconstructed over various scales, from transmission within households to exchange

between community and hospital environments, to inter-continental spread. Nuebel suggested that at the same time genome-wide evolutionary changes could be interpreted with respect to variation of phenotypic traits, including antimicrobial resistance and toxicity. He added that, as systems biology tools are being developed to extract relevant information from large genomic datasets, we are only beginning to understand the effects of genomic variation on virulence and on its regulation through complex genetic networks.

The role of flow cytometry in detecting carbapenemase-producing pathogens

Carbapenemase-producing pathogens are responsible for an increasing number of serious infections with high mortality rates. Carbapenemases are produced by multidrug resistant pathogens such as *Pseudomonas* spp, *Acinetobacter* spp and *Enterobacteriaceae*. Isabel Miranda (Porto, Portugal) presented a novel protocol for fast detection of carbapenemases based on flow cytometry (Miranda 2015). A total of 100 isolates (*Pseudomonas* spp, *Acinetobacter* spp and *Enterobacteriaceae*) phenotypically and molecularly well characterised were assayed by Miranda and her colleagues. Half of the strains were carbapenemase producers such as 20 KPC, 15 MBL, 15 OXA. ATCC, NCTC and CCUG type strains recommended by EUCAST were also included. Miranda explained that the screening test using flow cytometry (FACSCalibur cytometer) detected all carbapenemase-producing bacteria, and gave accurate negative results for the other strains. Using the protocol, the team correctly identified the type of carbapenemase in all the strains, including AmpC positive strains, exhibiting 100% of sensitivity and 100% of specificity.

Another recently proposed method for detection of carbapenemase production is the Blue-Carba test. This is based on the colour change of a pH indicator (bromothymol blue) resulting from imipenem hydrolysis by a carbapenemase. Speaking at ECCMID 2015, Angela Novais (Porto, Portugal) described the performance of the kit Rapid CARB Blue in comparison with the in-house Blue-Carba test using 73 carbapenemase-producing isolates from different *Enterobacteriaceae (E. coli, K. pneumoniae, E. cloacae)*, *Pseudomonas* spp. (*P. aeruginosa*, *P. pseudoalcaligenes*) and *Acinetobacter* spp. (*A. baumannii*, *A. pittii*, *A. haemolyticus*) species (Novais 2015).

Novais discussed the results of the study, which showed that all carbapenemase producers were detected by Blue-Carba test, which showed 100% sensitivity and 100% specificity. The Rapid CARB Blue kit revealed a high sensitivity (94.5%) and specificity (91.7%), and positive and negative predictive values of 98.6% and 73.3%, respectively. False negative results were obtained only for 4 *P. aeruginosa* or *A. baumannii* strains producing VIM-2, GES-6, OXA-23 or OXA-58.

The performance of the Carba NP test for the detection of carbapenemase-producing *Enterobacteriaceae* (CPE) was evaluated on a large set of enterobacterial isolates (n = 5,890) with decreased susceptibility to carbapenems. Laurent Dortet (Le Kremlin-Bicentre, France) presented the results of this study conducted from January 2012 to September 2014 (Dortet 2015). The Carba NP test was compared to a PCR-based detection of carbapenemase-encoding genes following by sequencing. Dortet explained that the Carba NP perfectly detected all carbapenemase producers of KPC-type, NDM-type, VIM-type, IMP-type, IMI-type, FRI-1 and all multiple carbapenemases producers. All OXA-48-like producers were efficiently detected except 3 OXA-48 (0.3% of OXA-48), 7 OXA-181 (19.4% of OXA-181) and 2 OXA-244 (100% of OXA232). Dortet concluded that while the Carba NP failed to identify about 20% of the OXA-181 producers which correspond a minor part (2.5%) of the OXA-48 type producing isolates identified in France, it led to detected FRI-1, a novel transferable carbapenemase of Ambler class A for which no molecular detection was available. The audience was reassured that the Carba NP test had an overall 99.2% sensitivity, 100% specificity, 100% positive predictive value and 99.7% negative predictive value for the detection of carbapenemase producing *Enterobacteriaceae* with reduced susceptibility of carbapenems (ertapenem).

There is a worldwide need for a rapid laboratory screening method for CPE, explained Catherine Denis (Antwerp, Belgium) (Denis 2015). Her team evaluated the performance of the Carba NP test (CNP) and the ROSCO Neo-Rapid CARB Screen (NRCS) kit. They selected and cultured 31 EB strains (4 KPC-, 4 KPC- plus VIM-, 2 NDM-, 2 VIM-, 1 IMP-, and 7 OXA-48-like enzyme-producing isolates, and 11 isolates expressing no or other beta-lactamases) using CNP and NRCS. Tests were read at 60 and 120 min, and 30, 60 and 120 min, respectively. Denis discussed the superiority of CNP for CPE screening compared to NRCS. The recently revised NRCS still did not meet adequate specificity criteria and, sometimes, could not be interpreted. CNP easily can be implemented in routine laboratories and represents a useful tool in the prevention of CPE spread, added Denis; but she warned that careful interpretation of CNP results is mandatory.

Isabelle Ote (Gembloux, Belgium) discussed CPR from the perspective of OXA-48, the most challenging resistance mechanism for diagnostic laboratories (Ote 2015). Ote and colleagues developed the OXA-48 *K*-SeT test, a new lateral flow assay that specifically detects OXA-48-like carbapenemases from bacterial colonies in less than 10 minutes. The OXA-48 *K*-SeT test was able to detect as low as 0.125 ng/ml of recombinant OXA-48 protein; it is highly specific for the detection of OXA-48 carbapenemase-producing strains, including its variants. It does not detect any other carbapenemase types (i.e. KPC, NDM, VIM and IMP). Tests were performed directly on bacterial colonies grown on solid medium after suspension in a specific buffer. The OXA-48 *K*-SeT test was able to detect OXA-48 directly from one single colony in less than 10 minutes. The limit of detection of the test is 1.5 10^6 CFU/ml when performed on serial dilutions of a suspension of OXA-48 producing *Klebsiella pneumonia* isolate. The OXA-48 *K*-SeT test is the first rapid identification confirmatory non-molecular assay for OXA-48 detection with results available within minutes.

Pierre Bogaerts (Yvoir, Belgium) described the electrochemical technique (BYG test) which detects CPE in less than 30 minutes (Bogaerts 2015). The BYG test is composed by a small in hand electronic device (the reader) and specifically prepared disposable electrodes; it includes a 10 µL loop of bacteria that is suspended in a lysis buffer with or without 3 mg/mL imipenem and directly transferred on the electrochemical cells. The signal is red as the subtraction between the signal values of the sample with and without imipenem. Bogaerts and his team assessed the BYG test in parallel with CarbaNP test using molecular results as Gold standard. The BYG test gave a positive result in less than 5, 10 and 15 minutes for 34, 5 and 1 isolates respectively. Comparatively, the CarbaNP test detected neither the 1 GES-6 nor 2 NDM-1-producing strains. Other tests discussed at ECCMID were the RAPIDEC CARBA NP test (RAPIDEC) and the MALDI-TOF MS assay.

Multi-drug resistance for high-risk clones

Rob Willems (Houten, Netherlands) discussed multi-drug resistance for *Staphylococcus aureus* and *Enterococcus* species risk clones from the perspective of genetic variation with a focus on the particular high-risk clones (HRC) for *Staphylococcus aureus*, *Enterococcus faecalis* and *Enterococcus faecium* (Willems 2015). He presented the HRC among health-care associated, methicillin-resistant *S. Aureus* (HA-MRSA) as CC5, 8, 22, 30 and 45 associated with global epidemics. A major issue presented by Willems was that whole genome sequencing-based phylogeny of ST239 (CC8) that is now circulating in large parts of the world showed intercontinental spread, although limited, followed by local clonal expansion and within hospital transmission. Willems explained that the number of clones for community-associated MRSA (CA-MRSA) is more diverse and includes CA-MRSA clones such as ST1, ST8 (USA300), which is the primary cause of skin and soft tissue infections in the U.S., ST30, ST59 and ST80.

The development of sequence-based typing methods, such as multilocus sequence typing (MLST) and, more recently, whole-genome sequence (WGS)-based typing, along with

rapid exchange of DNA sequence data via online databases, has led to the discovery of highly successful international clones and clonal complexes (CCs) among major Gram-negative bacterial pathogens. Mikhail V Edelstein (Smolensk, Russia) explained that despite frequent recombination and horizontal gene transfer that blur the boundaries between distinct clones, *Escherichia coli*, *Klebsiella pneumonia* and *Acinetobacter baumannii* reveal dominance of global clonal lineages and existence of intraclonal variants associated with particular virulence or drug resistance or combined virulence and resistance traits (Edelstein 2015). *Pseudomonas aeruginosa* shows an epidemic population structure with high clonal diversity and frequent recombination that cross wide geographic areas. Edelstein described the most noticeable examples of such MDR high-risk clones that seemed to have acquired resistance to various classes of antibiotics repeatedly and independently. *E. Coli* phylogroup B2 ST131 was associated with global spread of AmpCs and extended-spectrum beta-lactamases (ESBLs), particularly CTX-M-15, in the 1990s-2000s, and, more recently, of various carbapenemases (e.g., KPC, OXA-48 and NDM); *K. Pneumonia* ST258/ST512, ST11/ST340 of clonal group(CG)258 emerged as epidemic carbapenemase-producing clones in Europe, Asia and North America; *A. Baumannii* $CC1^{Pas}/CC109^{Oxf}$ and $CC2^{Pas}/CC92^{Oxf}$ encompass the vast majority of OXA-carbapenemase-producing *Acinetobacter* strains identified worldwide; and *P. aeruginosa* CC235, a pandemic clonal lineage associated with variety of acquired ESBLs and metallo-beta-lactamases. Edelstein underlined the importance of recognising the high-risk clones, understanding their epidemiology and biological mechanisms of adaptation in order to control the spread of drug resistance in Gram-negative pathogens.

Therapeutic developments in skin and soft tissue infection management

Healthcare provision is changing across Europe with most healthcare systems aiming to maximise the efficacy and cost-effectiveness of inpatient management. This year at ECCMID, the audience heard from a panel of European and US experts on the clinical and economic implications of skin and soft tissue infections (SSTIs) caused by Gram-positive bacteria in Europe, and the potential role of novel drugs in SSTI management in both Europe and the US.

Professor Christian Eckmann (Peine, Germany) presented an overview of the clinical and economic burden of SSTI treatment especially due to its considerable morbidity, mortality, resource utilisation, and costs (Eckmann 2015). SSTIs represent a significant proportion of antibacterial agents prescribed in hospitals. He explained that in Europe, SSTIs are the second most common indication for antibacterial use and are associated with high healthcare costs. For example, it costs €7835 per patient for initial treatment failure versus €4989 per patient for initial treatment success in Italy, while in Greece the total treatment costs per inpatient for MRSA SSTI was €2457-€3494 versus €7778-€8777 in France. Eckmann emphasised that Europe has overall longer hospital stays for the treatment of SSTIs compared to other world regions, and this results in higher healthcare costs and morbidities.

The U.S. experience was presented by George Sakoulas (La Jolla, California, USA), who informed the ECCMID audience that SSTIs are “one of the top 10 reasons for emergency room visits in the United States” (Sakoulas 2015). Sakoulas explained that in 2010 the US Food and Drug Administration (FDA) approved a new definition of acute bacterial skin and skin structure infections (ABSSSIs) ,which is different from a previous one of complicated SSSIs (cSSSIs), referring to cellulitis and erysipelas, wound infections and major cutaneous abscess of more than $75cm^2$ of surface area involvement. In the U.S., Sakoulas mentioned, outpatient antibiotic therapy is very much reliant on economically and logistically streamline treatment of ABSSSIs, and now the clinicians and patients can access new drugs recently approved by the U.S. FDA: tedizolid phosphate, dalbavancin, and oritavancin. Sakoulas described how tedizolid phosphate brings tolerability and safety improvements as well as reduced serotonergic and monoamine oxidase drug interaction

concerns to the oxazolidinone class of antibiotics. He further discussed clinical examples of using the new drugs to streamline ABSSSI therapy in outpatient settings.

Making a stand for Europe, Matthew Dryden (Winchester, United Kingdom) explained the contribution of new therapies to SSTI management and emphasised the current tendency to "overtreat less severe infections and undertreat the most severe infections"(Dryden 2015). The drugs used historically for the management of SSTI disease include penicillins, macrolides, licosamides and co-trimoxacozole; there are newer agents with activity against drug-resistant Gram-positive bacteria such as linezolid, daptomycin, oritavancin, dalbavancin, tezolid phosphate, while ceftaroline and tigecycline are now available for Gram-positive and Gram-negative bacteria. Dryden discussed the importance of selecting the most appropriate and efficacious therapeutic option and presented the details of outpatient parenteral antimicrobial therapy (OPAT) programmes, which work within the principles and standards of antimicrobial stewardship while allowing early hospital discharge. Dryden made the case for this programme as it will ease the pressure on hospital resources across Europe.

New agents for acute infections

Speaking at ECCMID 2015, Matteo Bassetti (Udine, Italy) emphasised the need for targeted use of new agents for acute infections and updated the audience on the "Bad Bugs, No Drugs" initiative from the Infectious Disease Society of America (IDSA), which was launched in 2004. Bassetti added that in 2014, this changed to "Bad Bugs, No Drugs, No ESKAPE" while the late-stage clinical development pipeline for problematic pathogens remained unacceptably lean (Bassetti 2015).

He called this the "paradox" of the antibiotic pipeline and the rise of resistance. For example, from 1983 to 1987, 16 new antibiotics became available, compared to only 2 in the period 2008-2012. There were no new Gram-negative agents available between 2010-2014, and no major classes of antibiotics were introduced between 1962-2000. However, the resistance rate for selected pathogens such as MRSA, *Enterococcus* resistant to vancomycin, *Candida* spp. resistant to fluconazole, *Acinetobacter* spp. resistant to imipenem has increased vastly over that period. The new classes of antibiotics introduced from 2000-2010 include oxazolidinones, lipopeptides and mutilins.

Bassetti explained the reasons for decreased antibiotic development over the past 10 year, whether economic (low price), regulatory or scientific (loss of expertise in R&D) and the unmet needs in the antibacterial pipeline. Mainly there is a need for broad and narrow spectrum drugs active against MDR Gram-negative rods, while Gram-positive drugs active against MRSA and Coagulase negative Staphylococcus have showed improved efficacy against osteomyelitis and endocarditis.

The IDSA has called for 10 new antibiotics by 2020 under the banner "Bad Bugs Need Drugs." Bassetti discussed the drugs currently available and those in development for *Staph. aureus* and Gram-negative bacilli. He focused on those agents in phase 3 such as novel beta-lactam plus approved inhibitor (ceftolozane-tazobactam) and approved beta-lactam plus novel inhibitor (ceftazidime-avibactam, ceftaroline-avibactam, aztreonam-avibactam, etc.). Ceftolozane/tazobactam is an antipseudomonal cephalosporin plus beta-lactamase inhibitor, currently completing phase 3 trials for treatment of cIAI and cUTI with an ongoing phase 3 trial in nosocomial pneumonia. Bassetti described the efficacy of ceftolozane as a potent penicillin-binding proteins (PBPs) inhibitor and compared its high affinity to that of ceftazidime and imipenem for all of the P aeruginosa PBPs. Tazobactam has in vitro coverage of the majority of extended spectrum beta-lactamsa (ESBL)-positive Enterobacteriaceae. Bassetti presented the benefits (predictable PK, rapid tissue distribution, renal excretion, safety data, high activity against ESBLs and PSA) and

negatives (no KPC activity, beta lactam allergic patients, no oral formulation for step-down therapy) of the ceftolozane/tazobactam combination. Another combination he discussed was ceftazidime/avibactam with its specific pros and cons.

Bassetti concluded that while the actual pipeline looks encouraging at least in theory, more clinical data in advanced phases is urgently needed.

Responsible use of antibiotics

Antibiotic use is widely regarded as a key driver for antimicrobial resistance (AMR). Michael Borg (Msida, Malta) explained that recent surveillance undertaken by the ECDC indicates that the European countries which report higher prevalence of AMR also tend to be those showing greater consumption of antibiotics (Borg 2015). Antibiotic stewardship (AS) is widely advocated as an important intervention to reduce AMR development. Borg pointed out that AS logically takes on even more importance in high-resistance countries. There are steps to be considered such as understanding and appreciating what drives high antibiotic prescribing in these countries where cultural factors have been proposed as major contributors. Making AS more effective in high-resistance countries will require that campaigns and strategies take into account the evidence base from medical research, behavioural science and change management. Borg emphasised that "copy and paste" approaches, using methodologies reported as effective in low-resistance countries having different cultural backgrounds are unlikely to succeed. He believes that the key to success is for interventions that are both informed by knowledge of the behavioural factors influencing prescribing and also are conducive to a country’s culture.

Timing of antibiotic prophylaxis prior to surgery

The current ASHP/IDSA guideline advises administration of antimicrobial prophylaxis prior to non-clean and implant surgery as within 60 minutes prior to incision (120 minutes for vancomycin and fluorquinolones due to prolonged infusion times). During a pros vs. cons debate on the timing of antibiotic prophylaxis prior to surgery, Marja Boermeester (Amsterdam, The Netherlands) made the case for prophylaxis and presented the evidence based on 13 observational studies that have been identified with SSI outcome comparing different timing intervals for surgical antibiotic prophylaxis (Boermeester 2015). There is low quality evidence that shows that administration prior to incision has significant benefit when compared to administration after incision in reducing SSI rate (OR 1.89 (1.05-3.4; p=0.03)). Also, low quality evidence shows that administration within 120 prior incision has significant benefit when compared to administration before 120 prior to incision in reducing SSI rate (OR 5.26 (3.29-8.39); p<0.0001). Low quality of evidence shows that administration within 60 min prior incision has neither benefit nor harm when compared to administration within 60- to 120 prior to incision in reducing SSI rate (OR 1.22 (0.92-1.61)). Boermeester explained that no recommendation can be made on the optimal timing interval within 60 minutes.

She described the current practice of anaesthesiologists to administer surgical antibiotic prophylaxis in the OR. This is often closer to incision within the 120-minute interval. The pharmacokinetics of the drugs allows the clinician to reduce the need for re-dosing in longer-lasting procedures as compared to administration closer to the 120 minutes. Boermeester added that it should not be difficult to implement an optimised timing for administration of antibiotic prophylaxis. When administered at surgical time-out, intervals should be reasonably within 120 minutes. While there are difficulties in adherence to recommended timing intervals, the use of SURPASS, a surgical safety checklist, has demonstrated to lead to better compliance with regard to timing of antibiotic prophylaxis. Other checklists like the WHO surgical safety checklist might help increase adherence to our recommendation as well.

Perils of travelling to endemic areas

Researchers that conducted a study that investigated fecal carriage and bacterial characteristics of ESBL-producing Enterobacteriaceae (EPE) in 11 people that travelled to endemic areas such as the Indian subcontinent, Southeast Asia, northern Africa and the Middle East, found that diarrhoea during the trip was significantly more common among the EPE positive participants, 19/49 (38.8%), compared to 22/108 (20.4%) in the negative group (P=0.02). The EPE-positive group had more contact with healthcare facilities and antimicrobial treatment during the trip in univariate analysis (P=0.005 and 0.035 respectively) (Vading et al. 2015). Malin Vading (Stockholm, Sweden) presented the results in the detected EPE isolates: *E. coli* (n=44), *Klebsiella pneumonia* (n=1) and *Citrobacter freundii (*n=1); all strains were resistant to cefotaxime. The researchers reported co-resistance: piperacillin-tazobactam 11, gentamicin 23, amikacin 2, ciprofloxacin 5 and trimethoprim-sulfametoxazole 28 isolates. Genes encoding aminoglycoside or quinolone resistance were seen in 22 isolates. Apart from fimH, found in 34 isolates, only 10 isolates carried any of the virulence factors. Vadig concluded that the risk of intestinal colonisation with EPE is significant when traveling to India and northern Africa and elevated also when traveling to Southeast Asia or the Middle East.

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