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Letter to the Editor

Infection with multiple carbapenemase-producing bacteria following cosmetic surgery in Iran detected after the introduction of systematic screening of repatriates

Sir,

The business of medical tourism is growing, including travel abroad to access medical services such as cosmetic surgery [1]. This raises concerns regarding the burden for the domestic healthcare system owing to the spread of multidrug-resistant bacteria [2], as popular destinations include countries with a high prevalence of antimicrobial resistance.

Systematic screening for carbapenemase producing organism (CPO), methicillin resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) has been introduced to our hospitals in Copenhagen, Denmark, for patients who have been hospitalised outside of the Nordic countries within the past 6 months. Here we report the case of a patient colonised and infected with three distinct CPO and a VRE following cosmetic surgery in Iran.

ESwab™ was used to collect specimens from the nares, pharynx, rectum and wounds. Specimen were incubated overnight in four selective enrichment broths and were subsequently plated on selective chromogenic agar, including chromID® CARBA SMART (bioMérieux, Marcy-l'Étoile, France), Brilliance MRSA 2 (Oxoid Deutschland GmbH, Wesel, Germany) and CHROMagar™ VRE (CHROMagar, Paris, France). Bacterial identification was performed by matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF/MS) (MALDI Biotyper; Bruker, Bremen, Germany).

Minimum inhibitory concentrations (MIC) were determined by the microbroth dilution method (Sensititre™; Thermo Fisher Scientific, Roskilde, Denmark) and were interpreted using European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints (http://www.eucast.org). The colistin MIC for the colistin-resistant isolate was re-tested using Micronaut MIC Strip (BioConnections, Knypersley, UK). For fosfomycin and one re-test (marked with '[b]' in Table 1), gradient strip was used (Etest; bioMérieux). Genomic DNA was extracted using a DNeasy® Blood & Tissue Kit (QIAGEN, Copenhagen, Denmark) for whole-genome sequencing. Fragment libraries were constructed using a Nextera Kit (Illumina, Little Chesterford, UK) followed by 251-bp paired-end sequencing (MiSeq™; Illumina). Data were assembled using CLC Bio Genomics Workbench 7.5 (QIAGEN, Aarhus, Denmark). KmerResistance 2.0 (http://www.genomicepidemiology.org) and NCBI Blastx (https://blast.ncbi.nlm.nih.gov/Blast.cgi) were used to identify acquired antimicrobial resistance genes. Chromosomal mutations associated with fluoroquinolone and colistin non-susceptibility were identified using software developed in-house.

A Danish resident with Iranian ethnicity travelled to Iran for cosmetic surgery. The procedures included nose correction, abdominal liposuction and breast surgery. The operations were complicated by iatrogenic perforation of the small intestine, necessitating resection of the intestine with establishment of an anastomosis. Further complications included tissue necrosis in the abdominal wall requiring multiple re-operations as well as post-operative pneumonia, both treated with prolonged broad-spectrum antimicrobial therapy. After 4 weeks of hospitalisation the patient was transferred to a Danish hospital with significant discharge of intestinal secretions from drainage holes, wound dehiscence with visible intestines and multiple fistulas. At arrival, screening samples were taken and isolation precautions were applied. The patient underwent surgical revision of abdominal abscesses and loop enterostoma. After 2 months of admission, the patient was transferred to a short bowel unit for education in parenteral nutrition.

An NDM-1- and OXA-48-producing *Klebsiella pneumoniae*, an OXA-48-producing *Escherichia coli* and an OXA-23-producing *Acinetobacter baumannii* were detected in screening samples and later clinical samples recovered during surgery (Table 1). The *K. pneumoniae* isolate was susceptible only to tigecycline and chloramphenicol. Despite phenotypic resistance to colistin, acquired resistance genes (*mcr-1*, *-2*, *-3* or *-4*) were not detected. No amino acid changes were detected in the chromosomal genes *mgrB*, *ompK35*, *phoP*, *phoQ*, *pmrA*, *pmrB* and *lpxM*, but an N212T mutation was found in the *yciM* gene. The gene is thought to be involved in lipopolysaccharide synthesis, and another amino acid change in *yciM* (V43G) has recently been suggested to be linked to colistin resistance [3]. However, the N212T mutation has not been linked to reduced susceptibility to colistin prior to the current study and needs to be investigated further before its contribution to colistin resistance can be determined. The *E. coli* isolate was phenotypically susceptible to meropenem (MIC = 0.5 mg/L) but harboured the carbapenemase gene $bla_{\text{OXA-48}}$. Apart from the three CPOs, a *vanA*-positive *Enterococcus faecium* was identified. No MRSA was detected in the patient.

Because of excellent response to surgery, antibiotic therapy covering extensively drug-resistant bacteria was withheld.

Here we describe a patient colonised and infected with three distinct CPO and a VRE after cosmetic surgery in Iran. These included a *K. pneumoniae* harbouring both $bla_{\text{NDM-1}}$ and $bla_{\text{OXA-48}}$ and resistant to colistin, leaving very limited antibiotic treatment options. Travel to endemic countries is a major risk factor for colonisation and infection with multidrug-resistant bacteria, and medical tourists are at risk for healthcare-associated infections [1,4]. Cases of repatriates from endemic countries harbouring multiple CPO have been reported from other low-prevalence

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Table 1
Phenotypic and molecular characterisation of the three carbapenemase-producing organisms.

Antimicrobial class/ agent	*Klebsiella pneumoniae* (ST147)		*Escherichia coli* (ST131)		*Acinetobacter baumannii* (ST352)	
	MIC [SIR]	ARGs	MIC [SIR]	ARGs	MIC [SIR]	ARGs
β-Lactams						
TZP	>64/4 [R]	**bla_{NDM-1}**, **bla_{OXA-48}**, $bla_{CTX-M-15}$, bla_{OXA-1}, bla_{SHV-12}, bla_{TEM-1B}	>64/4 [R]	**bla_{OXA-48}**, $bla_{CTX-M-15}$, bla_{TEM-1B}	>64/4 [IE]	**bla_{OXA-23}**, bla_{ADC-25}, bla_{OXA-66}, bla_{PER-1}
TCC	>128/2 [R]		>128/2 [R]		>128/2 [IE]	
Cefotaxime	>32 [R]		>32 [R]		>32[a]	
Ceftriaxone	>32 [R]		>32 [R]		>32[a]	
Ceftazidime	>16 [R]		8 [R]		>16[a]	
Cefepime	>16 [R]		8 [R]		>16[a]	
Aztreonam	>16 [R]		>16 [R]		>16[a]	
Ertapenem	>4 [R]		2 [R]		>4[a]	
Imipenem	>8 [R]		2 [S]		>8 [R]	
Meropenem	>8 [R]		0.5[b] [S]		>8 [R]	
Doripenem	>2 [R]		0, 25 [S]		>2 [R]	
Aminoglycosides						
Gentamicin	>8 [R]	*aac(6′)-Ib*-cr, *aac(3)-II*, *aadA5*, *rmtC*	>8 [R]	*aac(3)-IId*-like, *aadA5*, *strA*, *strB*	>8 [R]	*aac(3)-Ia*-like, *aph(3′)-VIa*-like, *aph(3′)-VIb*-like, *strA*, *strB*
Amikacin	>32 [R]		≤4 [S]		>32 [R]	
Tobramycin	>8 [R]		4 [I]		≤1 [S]	
Fluoroquinolones						
Ciprofloxacin	>2 [R]	*aac(6′)-Ib*-cr, *oqxA*-like, *oqxB* (*gyrA* S83I, A84DEL; *parC* S80I)	>2 [R]	(*gyrA* S83L, D87N; *parC* S80I, E84V; *parE* I529L)	>2 [R]	
Levofloxacin	>8 [R]		>8 [R]		>8 [R]	
Other antibiotic classes						
Tigecycline	≤0.25 [S]		≤0.25 [S]		2 [IE]	
SXT	>4/76 [R]	*sul1*, *dfrA17*	>4/76 [R]	*sul1*, *sul2*, *dfrA17*	>4/76 [R]	*sul2*
Chloramphenicol	4 [S]	*catB4*	8 [S]		>16[a]	
Colistin	>64 [R]	(*yciM* N212T)	≤0.25 [S]		0.25 [S]	
Fosfomycin[b]	128 [R]	*fosA*-like	2 [S]		128[a]	

ST, sequence type; MIC, minimum inhibitory concentration; S, susceptible; I, intermediate; R, resistant; ARG, antimicrobial resistance gene; TZP, piperacillin/tazobactam; TCC, ticarcillin/clavulanic acid; SXT, Trimethoprim/sulfamethoxazole; IE, insufficient evidence that the organism is a good target for therapy with the agent according to EUCAST; EUCAST, European Committee on Antimicrobial Susceptibility Testing. Carbapenemases are in bold type.
[a] Susceptibility testing not recommended according to EUCAST.
[b] MIC testing performed with gradient strip.

countries [5], including reports of complications following cosmetic surgery in endemic areas. The accurate extent of medical tourism is unknown but is estimated to involve 1.6 million Americans [4] and is an expanding industry. A systematic assessment of the extent and consequences is needed.

Systematic screening strategies of patients at cross-border transfer from high-prevalent countries is recommended and the case report described here highlights the importance of this strategy to prevent international spread of antimicrobial resistance.

Competing interests

BJH has received personal fees from MSD outside of the submitted work. All other authors declare no competing interests.

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Ethical approval

Written consent was obtained from the patient.

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