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ORIGINAL ARTICLE

Extensive colonization with carbapenemase-producing microorganisms in Romanian burn patients: infectious consequences from the Colectiv fire disaster

L. E. Pirii[1] · A. W. Friedrich[1] · J. W.A. Rossen[1] · W. Vogels[2,3] · G. I. J. M. Beerthuizen[4] · M. K. Nieuwenhuis[5] · A. M. D. Kooistra-Smid[1,2] · E. Bathoorn[1]

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Abstract Health care of severe burn patients is highly specialized and may require international patient transfer. Burn patients have an increased risk of developing infections. Patients that have been hospitalized in countries where carbapenemase-producing microorganisms (CPMO) are endemic may develop infections that are difficult to treat. In addition, there is a risk on outbreaks with CPMOs in burn centers. This study underlines that burn patients may extensively be colonized with CPMOs, and it provides best practice recommendations regarding clinical microbiology and infection control. We evaluated CPMO-carriage and wound colonization in a burn patient initially treated in Romania, and transported to the Netherlands. The sequence types and acquired beta-lactamase genes of highly-resistant microorganisms were derived from next generation sequencing data. Next, we searched literature for reports on CPMOs in burn patients. Five different carbapenemase-producing isolates were cultured: two unrelated OXA-48-producing *Klebsiella pneumoniae* isolates, OXA-23-producing *Acinetobacter baumanii*, OXA-48-producing *Enterobacter cloacae*, and NDM-1-producing *Providencia stuartii*. Also, multi-drug resistant *Pseudomonas aeruginosa* isolates were detected. Among the sampling sites, there was high variety in CPMOs. We found 46 reports on CPMOs in burn patients. We listed the epidemiology of CPMOs by country of initial treatment, and summarized recommendations for care of these patients based on these reports and our study.

Keywords Carbapenemase · CPE · Burn patients · Infection control · Review · Molecular epidemiology

✉ L. E. Pirii
l.e.pirii@umcg.nl

[1] Department of Medical Microbiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[2] Department of Medical Microbiology, Certe, Groningen, The Netherlands

[3] Department of Medical Microbiology, Martini Hospital, Groningen, The Netherlands

[4] Burn Centre Martini Hospital, Groningen, The Netherlands

[5] Association of Dutch Burn Centers, Burn Centre, Martini Hospital Groningen, Groningen, The Netherlands

Introduction

In October 2015, the crowded nightclub Colectiv in Bucharest, Romania caught on fire due to indoor use of pyrotechnics. In total, 64 visitors died from burn wounds and/or inhalation of smoke, and 144 were injured. The injured visitors were immediately transported to 12 nearby hospitals in Bucharest and Ilfov County for medical care [1]. Since appropriate medical care could not be provided for all patients, international aid was requested. About 80 patients were transported to various countries, including 16 to The Netherlands and Belgium, after they had been hospitalized for over a week in Romania.

Romania is a country with a high prevalence of carbapenemase-producing microorganisms (CPMO) [2, 3]. As burn patients have a high risk of developing infectious complications, this is a serious problem to be reckoned with. Wound infection with CPMO complicates the treatment of patients with burns [4, 5]. Patients suffering from these kind of infections have to be treated with last-line antibiotic schemes. These schemes are most often sub-optimal for treatment of the infection and have more adverse effects. In addition to the impact of CPMO-infection on the treatment of the

individual patient, the introduction of CPMOs in the hospital also may lead to nosocomial transmission of CPMO resulting in hospital outbreaks.

Burn wounds are highly prone to long-term colonization by nosocomial bacteria. It has been reported that in more than 90% of patients the wounds were colonized by the seventh day, and that constitution of colonizing microorganisms in individual burn wounds changes over time [6, 7]. Wound colonization can subsequently result in severe invasive infection, a leading cause of mortality in patients with burn injury [8].

Restrictive and targeted use of antibiotics is important in treatment of burn patients, in particular in those with CPMOs. Guidelines from the European Burns Association recommend the use of "topical creams with good antimicrobial effects without the risk for resistance or allergy". "The use of prophylactic systemic antibiotics is not supported by evidence" [9, 10]. Infections are most often caused by the microorganisms that colonize the burn wounds [11, 12]. Thus, it is important to culture wounds on admission, also before signs of infection, to know which antibiotics to start in case of infection.

Here, we describe the diversity in CPMO cultured at admission from several burn wounds and body sites in a burn patient from the Colectiv fire disaster transported to a dedicated Burn Centre in the Netherlands. Next, we performed an analysis of literature focusing on CPMO in patients with burns. By this, we show that the presented case of extensive burn wound colonization with CPMO is not an exception. Finally, we provide specific recommendations for medical care of burn patients transported from CPMO endemic regions to other countries with low CPMO prevalence. For non-endemic countries such as the Netherlands, international transfer of patients carrying CPMOs imposes a risk on dissemination to other hospitalized patients.

Case description

A Romanian victim of the Colectiv fire disaster had been admitted to "Spitalul Clinic de Urgenta" in Bucharest on October 31st 2015 with a total body surface area (TBSA) burn of approximately 30%. The patient was in his 20s and had an uncomplicated medical history before this incident.

There were IIA–IIB degree burn lesions on the face, posterior cervical area, right scapular area, deltoid area bilaterally and IIB–III degree burns on both hands, forearms, and scalp. Meshed split skin grafting had been performed to cover the burns on his right lower arm and hand. On the IC unit, the patient had received broad-spectrum empirical antibiotic therapy with Piperacillin/ Tazobactam 4.5 g tid and Linezolid 600 mg bid. Based on results of wound cultures that revealed *Acinetobacter spp.*, antibiotics were switched to Colistin 2 million units tid for the treatment of wound infection. For topical treatment of the wounds, silversulfadiazine, kanamycine ointments, and betadine scrub were used. No additional information on the microbiological cultures was mentioned in the Romanian discharge notes.

The patient was transported by airplane and ambulance to the Burn Centre of the Martini Hospital (BCMH) in Groningen, The Netherlands on November 7th 2015, 7 days after the incident. Upon admission to the BCMH, the patient's TBSA burned was still approximately 10%. Admission cultures taken from the wounds and body sites (nose, throat, perineum) showed extensive colonization with CPMOs (see results section). Following regular Dutch infection control recommendations, the patient was consequently placed in isolation. However, in this phase there was no need for treatment with systemic antibiotics. The burn wounds were topically treated with silversulfadiazine ointment. After 12 days, definitive covering of non-healing sites was opportune after enlargement of autologous donor skin in a ratio of 1:1.5. Skin defects on both hands and ears were covered with skin grafts taken from the right upper leg. Good take of the grafts was observed in the weeks after surgery. Pressure gloves were used to augment the healing of the hands. Through extensive physical and occupational therapy, the patient regained his ability to perform normal daily activities. The patient was discharged from the hospital after 34 days.

After discharge, the patient's air-locked room with sanitary facility was disinfected. Subsequently taken environmental samples were negative.

Methods

Culture and characterization of bacterial isolates

Upon admission, screening throat, nose, perineum, rectum, and wound sample cultures were taken for detection of MRSA and highly-resistant gram negative bacteria (HRGN). Cultures from wounds were taken from the following locations: the anterior left elbow, the left and right ear, right shoulder and the left groin on November 9th; the left palm, and right upper back side on November 16th; the dorsum of the left hand, the right fingers and a repeated culture of right and left ear on November 30th. In total, 29 cultures were taken during the hospital stay: 14 screening cultures, three urine cultures, and 12 wound cultures. Burn wounds were cultured using sets of RODAC plates with five different media: blood agar +5% sheepblood (BA + 5%SB), colistin oxolinic-acid blood agar, mannitol salt agar, MacConkey agar no.3 + crystalviolet, Sabouraud dextrose agar + aztreonam/vancomycin (Mediaproducts, the Netherlands). For sampling, the plates were applied directly on the wounds. The plates were incubated for 48 h at 35 °C. Screening for methicillin-resistant *Staphylococcus aureus* (MRSA) was done with Xpert MRSA Gen3 assay (Cepheid, France) and by culture using

BA + 5%SB and CHROMagar ID MRSA (bioMérieux, France) plates. Species determination of isolates was performed by using Maldi-TOF MS (bioMérieux, France). Antibiotic susceptibility was tested using VITEK 2 XL (bioMérieux, France). Minimal inhibitory concentrations (MICs) to tigecyclin, amikacin, and fosfomycin were tested using Etests according to manufacturer's guidelines on Mueller Hinton agar (AB Biodisk, Germany). Susceptibility was interpreted according to EUCAST guidelines [13]. Using whole genome sequencing data, we characterized the CPMO isolates and identified acquired resistance genes as described before [14]. In short, genomic DNA was extracted and prepared libraries were run on a MiSeq platform (Illumina, USA) generating paired-end 250-bp reads. De novo assembly of paired-end reads was performed using CLC Genomics Workbench v7.5 (QIAGEN, Germany) after quality trimming (Qs ≥ 20) with optimal word size. The acquired antimicrobial resistance genes were identified by uploading assembled genomes to the Resfinder server v2.1 [15]. The MLST-types were assessed using SeqSphere v3.4.0 (Ridom GmbH, Germany).

Patient informed consent and approval of local ethical committee have been obtained. All of the assessed culture samples were taken in routine diagnostics.

Literature analysis

We performed a literature search in PubMed to assess the epidemiology of CPMOs in burn wound care and recommendations for care of these patients by the following search strategy: ((burn[MeSH] OR burn*[TIAB] OR burn*[All Fields])) AND ((carbapenemase[MeSH] OR carbapenemase[All Fields] OR carbapenem resistant[MeSH] OR carbapenem resistant[All Fields] OR carbapenemase producing organisms[MeSH] OR carbapenemase producing organisms[All Fields] OR carbapenemase producing Enterobacteriacae[MeSH] OR carbapenemase producing Enterobacteriacae[All Fields] OR panresistant[MeSH] OR panresistant[All Fields] OR carbapenemase producing microorganisms[MeSH] OR carbapenemase producing microorganisms[All Fields])). Studies up to December 2016 were retrieved and screened by their title and abstract for their relevancy on the topic.

Results

Cultures

MRSA diagnostics were all negative; methicillin-susceptible *S. aureus* was cultured from nose and the burn wounds. We present an overview of characteristics of the isolated HRGNs in Table 1. In total, six different HRGNs were detected: five different carbapenemase-producing isolates, and one carbapenem-resistant *Pseudomonas aeruginosa* isolate. The carbapenemase-producing isolates included OXA-48-producing *Klebsiella pneumoniae* isolates of ST type 147, and 395, OXA-23-producing *Acinetobacter baumanii* ST type 231, OXA-48-producing *Enterobacter cloacae* ST type 114, and NDM-1-producing *Providencia stuartii*.

An overview of all body locations and isolated HRGNs is presented in Fig. 1. Screening cultures for carriage of HRGNs were positive in nose (4 different isolates), perineum (3 different isolates), rectum (1 isolate) and throat (1 isolate). Cultures from the wound sites showed varying colonization with HRGNs. All sampled wound sites were colonized by HRGNs. The highest number of HRGNs 5/6 were isolated from the groin wound, a donor site wound after the grafting procedures done in Romania. The MDR *Pseudomonas aeruginosa* isolates were exclusively detected in samples from the upper body. We observed differences in colonization in similar body regions: the right forearm was positive for single isolates of highly-resistant *Enterobacter cloacae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumanii*, whereas the left forearm sample grew *Klebsiella pneumoniae*. The matching culture results between urine and both hands are remarkable: in all three samples the NDM-1-producing *Providentia stuartii* were cultured.

All isolates tested resistant to cotrimoxazol, ciprofloxacin and aminogycosides, except for *Klebsiella pneumoniae* isolates of ST 395 and OXA-48-producing *Enterobacter cloacae* which were susceptible to amikacin. Only the NDM-1 producing *Providencia stuartii* NDM-1 and *Klebsiella pneumoniae* ST type 147 were susceptible to fosfomycin. Two colistin-resistant isolates were detected: an OXA-48-producing *Providencia stuartii*, which is intrinsically resistant, and an NDM-1-producing *Klebsiella pneumoniae*.

In addition, multiple carbapenem-non-susceptible *Pseudomonas aeruginosa* isolates of MLST ST235 were grown. The *Pseudomonas* isolates were multidrug resistant, testing resistant to antipseudomonal beta-lactams, fluorquinolones, and aminoglycosides, and susceptible to colistin.

Review

In our review search we found 84 reports on CPMOs in burn wound care. Of these, 38 were off-topic, thus we included 46 reports. To assess the epidemiology, we present a country by country overview (Table 2) of reports on CPMOs in burn care centers. The country of initial care is shown.

CPMOs in burn patients have been reported from institutions over all continents.

The CPMOs included *Acinetobacter baumanii, Pseudomonas aeroginosa,* and the following Enterobacteriaceae: *Escherichia coli, Klebsiella oxytoca* and

Table 1 Characteristics of the isolated highly-resistant Gram negative bacteria (HRGNs)

Isolate	Date	Sample	MIC MER	MIC IMP	Sensitivity					MIC COL	MIC TIG	*Bla*-genes[a]	ST type
			(mg/L)	(mg/L)	AK	GN	SXT	CIP	FOS	(mg/L)	(mg/L)		
A. baumanii	30–11-2015	Left ear	> = 16 R	> = 16 R	R	R	R	R	R	<=0.5 S	3 R	OXA-23; OXA-64	ST 231
E. cloacae	7–11-2015	Perineum	8 I	> = 16 R	S	R	R	R	R	<0.5 S	2 R	OXA-48; CTX-M 15; OXA-1; TEM-1b; ACT-16	ST 114
K. pneumoniae	9–11-2015	Right ear	> = 16 R	> = 16 R	R	R	R	R	S	> = 16 R	3 S	OXA-48; CTX-M-15; OXA-1; NDM-1; TEM-1b	ST 147
K. pneumoniae	7–11-2015	Perineum	> = 16 R	> = 16 R	S	R	R	R	R	<=0.5 S	1.5 S	OXA-48; CTX-M 15; OXA-1; TEM-1b; SHV-11	ST 395
K. pneumoniae	30–11-2015	Perineum	> = 16 R	> = 16 R	S	R	R	R	R	<=0.5 S	1,5 S	OXA-48; CTX-M-15; OXA-1; TEM-1b; SHV-11	ST 395
K. pneumoniae	7–11-2015	Rectum	>32 R	12 R	S	R	R	R	R	<=0.5 S	2 R	OXA-48; CTX-M 15; OXA-1; TEM-1b; SHV-11	ST 395
P. stuartii	9–11-2015	Left groin	> = 16 R	> = 16 R	R	R	R	R	S	>16 R	3 R	NDM-1; OXA-10; CMY-4	n.a.
P. stuartii	23–11-2015	Perineum	> = 16 R	> = 16 R	R	R	R	R	S	> = 16 R	Not tested	NDM-1; OXA-10; CMY-4	n.a.
P. stuartii	23–11-2015	Urine	>16 R	> = 16 R	R	R	R	R	S	> = 16 R	Not tested	NDM-1; OXA-10; CMY-4	n.a.
P. stuartii	30–11-2015	Perineum	2 S	> = 16 R	R	R	R	R	S	> = 16 R	Not tested	NDM-1; OXA-10; CMY-4	n.a.
P. aeruginosa	7–11-2015	Throat	2 S	2 S	R	R	Not tested	R	R	0.5 S	Not tested	None detected	ST 235
P. aeruginosa	23–11-2015	Throat	4 I	1 S	R	R	Not tested	R	R	<=0.5 S	Not tested	None detected	ST 235
P. aeruginosa	30–11-2015	Left dorsum hand	3 I	2 S	R	R	Not tested	R	R	<=0.5 S	Not tested	None detected	ST 235

ak amikacin, *gn* gentamicin, *sxt* trimethoprim/sulfamethoxazole, *cip* ciprofloxacin, *fos* fosfomycin, *tig* tigecycline, *col.* colistine, *n.a.* not available

[a] Acquired beta-lactamase genes are presented

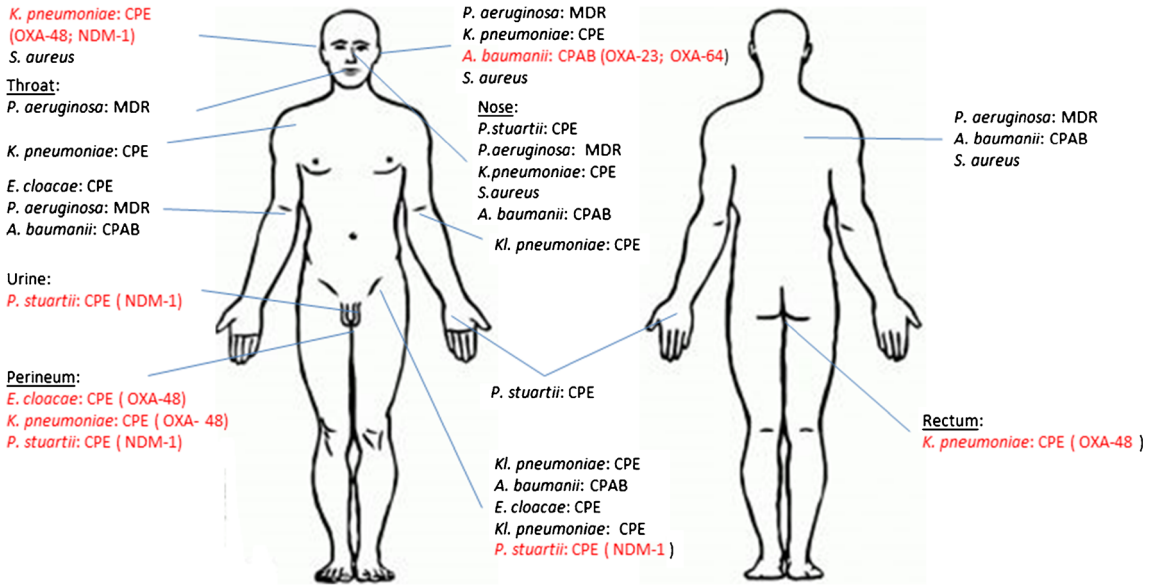

Fig. 1 Overview of all body locations and isolated HRGNs. *CPE* Carbapenemase producing Enterobacteriacae, *CPAB* Carbapenemase producing Acinetobacter baumanii, *MDR* Multidrugresistant

Klebsiella pneumoniae, Enterobacter cloacae, and *Providencia stuartii.* In these CPMOs, carbapenemase subtypes of KPC, NDM, VIM, IMP and OXA were detected.

The highest number of reports originated from Iran. In 17 publications, patients with burns hospitalized in Iran with carbapenem-resistant *Acinetobacter baumanii* and *Pseudomonas aeruginosa* were reported. The great diversity of carbapenemases detected in *Acinetobacter baumanii* in the Iranian studies is remarkable. One isolate even produced KPC, VIM and OXA-23, representing three different carbapenemases [39].

With our search, we retrieved two studies that described victims of the Colectiv fire disaster from Romania who were treated in England. As in our study, each of them was colonized and or infected with an extraordinary diversity of CPMOs. NDM-producing *Klebsiella pneumoniae*, OXA-48-producing *Klebsiella pneumoniae* and *Escherichia coli*, OXA-40-producing *Acinetobacter baumanii* and carbapenem-resistant *Pseudomonas aeruginosa* were isolated from these patients [13, 14]. The prolonged duration of hospitalization in Romania may have contributed to this extensive colonization with CPMOs. No transfer information had been given to their service about previous microbiology results. One of their patients died of pan-resistant NDM-producing *Klebsiella pneumoniae* septicemia within 48 h of admission. A second case died from severe sepsis due to extensive infected burn injuries: a pan-resistant OXA-48-producing *Klebsiella pneumoniae* grew in the blood culture. Our patient fortunately did not develop infections requiring treatment with systemic antibiotics. Nonetheless, we proactively tested antibiotic susceptibilities for last-line treatment options in all the isolates.

Recommendations

The Netherlands is a non-endemic country for CPMOs. To maintain this status, we put maximum effort in surveillance and infection control to prevent unnoticed introduction and dissemination of CPMOs. Experience with treatment of burn patients from endemic countries in countries with low CPMO prevalence has been described in six studies [18, 19, 26, 28, 56, 57]. In Table 3, we provide an overview of advice based on these studies completed by recommendations from the present study. All of the studies were alert for the serious risk of CPMO-carriage in transferred patients after hospitalization abroad. Outbreaks with CPMO or outbreak strains or evaluation of contact precautions after an outbreak were described in eight studies [19, 23, 26, 27, 51, 57, 62, 63]. To reduce the risk of transmission of CPMO, patients should be treated in contact isolation in single-patient rooms until culture results are known. Not only can bacteria spread directly by hand contacts [28, 64–66], but also indirectly through the environment and by medical equipment [28, 56, 64–66]. Therefore, we recommend standardized guidelines for the transfer of severely-ill patients between European countries, where detailed procedures on communication, screening and infection prevention measures are described. Especially for specific treatment and in case of international help, clinical staff organizing treatment abroad need to be aware of such guidelines. Furthermore, we recommend education of staff in hand hygiene and isolation precautions, enhancement of disinfection of patient rooms, and single-use of medical equipment if feasible for treatment of burn patients. When transmission of CPMOs is suspected, isolates should be typed and their molecular

Table 2 Review of reported carbapenem-resistant bacterial species isolated from burn patients with the country of initial care

Country	Study	Species	Carbapenemase
Afghanistan	[16]	*P. stuartii*	NDM-1
	[16]	*P. aeruginosa*	VIM-1
Algeria	[17, 18]	*P. aeruginosa*	NDM-1; VIM-4
	[18, 19]	*A. baumanii*	OXA-23
Bulgaria	[20]	*P. aeruginosa*	n.r.
	[20]	*A. baumanii*	n.r.
Brazil	[21]	*P. aeruginosa*	n.r.
China	[22–24]	*P. aeruginosa*	IMP-4; VIM-2
	[24, 25]	*A. baumanii*	OXA-23
	[24]	*K. pneumoniae*	n.r.
Egypt	[26]	*A. baumanii*	n.r.
France	[27]	*A. baumanii*	OXA-58
India	[28]	*K. pneumoniae*	OXA-48&NDM
	[29, 30]	*P. aeruginosa*	n.r.
	[30]	*A. baumanii*	n.r.
Iran	[31–41]	*A. baumanii*	KPC&VIM&OXA-23; VIM&OXA-23; KPC&OXA-23; OXA-23; OXA-40; OXA-23&OXA-40; OXA-23& OXA-58; OXA-23&OXA-40&OXA-58; OXA-40&OXA-58; OXA-23&OXA-58; OXA-143; OXA-58; OXA-23&OXA-24; OXA-24; KPC; VIM
	[41–47]	*P. aeruginosa*	IMP&VIM; IMP; VIM; KPC; AIM
	[41, 48, 49]	*K. pneumoniae*	KPC
Israël	[7]	*P. aeruginosa*	n.r.
	[7]	*A. baumanii*	n.r.
	[7, 50]	*K. pneumoniae*	KPC-3
Italy	[51]	*A. baumanii*	n.r.
Libya	[52]	*A. baumanii*	OXA-23 like; NDM-1
Morocco	[19]	*A.baumanii*	n.r.
Mongolia	[53]	*A. baumanii*	OXA-58
		P. aeruginosa	VIM-2
Pakistan	[28, 54]	*K. pneumoniae*	OXA-48&NDM; OXA-48
	[28]	*P. stuartii*	NDM
		P. aeruginosa	VIM
		K. oxytoca	NDM
		E. coli	OXA-48&NDM
		A. baumanii	OXA 23
Poland	[55]	*A. baumanii*	OXA-23 like; OXA-40 like
Romania[a]	This study, [28, 56]	*A. baumanii*	OXA-40; OXA-23
	[28]	*E. coli*	OXA-48
	[56]	*P. aeruginosa*	n.r.
	This study, [56]	*K. pneumoniae*	OXA-48&NDM-1; OXA-48
	This study	*P. stuartii*	NDM-1
	This study	*E. cloacae*	OXA-48
Tunisia	[57–59]	*P. aeruginosa*	VIM-2
	[19]	*A.baumanii*	OXA-23 like
Turkey	[60]	*P. aeruginosa*	n.r.
	[60]	*A. baumanii*	n.r.
USA	[61]	*E. cloacae*	KPC-3
	[61, 62]	*K. pneumoniae*	KPC
	[63]	*A. baumanii*	OXA-40

Carbapenemase types/subtypes are shown if tested

n.r. no carbapenemase genotyping reported

Some isolates produce multiple carbapenemases. Carbapenemase combinations are noted by "&"

[a] All Romanian studies are on victims of the Colectiv fire disaster

characteristics should be compared to confirm the clonal spread. Based on this, an outbreak investigation should be started. Control of CPMO or the roll-back of CPMO is today one of the most important goals.

Table 3 Recommendations concerning medical microbiology and infection control in treatment of burn wound patients

Recommendations	References
Screening/surveillance of patients on admission (throat, nose, rectum, perineum,) on HRMOs	[64, 65, 67], this study
Sampling of various burn wound sites	This study
Molecular characterization of isolates	This study
Treatment in isolation until cultures are negative for HRMOs	[62, 64, 65, 67]
Proactively testing of antibiotic options	[64, 65], this study
Antimicrobial stewardship/ No systemic antibiotics as prophylaxis	[20, 64, 65, 67], this study
Good communication of the microbiological results	This study
Staff education/ensuring optimal compliance in hand-hygiene and isolation precautions	[20, 28, 62, 64–67]
Enhanced environmental disinfection and environmental sampling following the terminal cleaning	[20, 28, 56, 64–66]
Single use or effective decontamination of medical equipment going from one patient to another	[28]

Samples of throat, nose, rectum, perineum, and all wound sites should be taken at admission to detect all CPMOs and MRSAs carried by the patient. It is important to detect all CPMOs and test their susceptibility patterns, so that targeted therapy can be started in case of systemic infections. Ideally, treating clinicians should already be informed upon patient admission about culture results from the hospital of discharge. For this purpose, good communication within health care networks is needed. This is may be facilitated by the European Burns Association.

To summarize, we showed that burn patients that have been hospitalized in a CPMO endemic country can be colonized by an extensive variety of CPMOs. CPMO presence may differ among body locations, thus we recommend culturing of multiple wound sites. Burn wound colonization by CPMOs is a worldwide problem. There is a high risk for burn patients to develop invasive infections by CPMOs, which require targeted antibiotic therapy. In addition, there is the risk on hospital outbreaks by these CPMOs. Therefore, medical care facilities treating patients with burns transported from endemic regions should have advanced medical microbiology, and infection control systems in place to detect CPMOs, treat infections, and prevent onward transmission.

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