A patient with sepsis following a burn injury in Pakistan

A female patient in her forties was transferred to the Burn Centre at Haukeland University Hospital four weeks after a severe burn injury in Pakistan. During the next two days she developed sepsis and multi-organ failure.

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During her stay in Pakistan, a Norwegian female patient, in her forties, suffered burns to 30–35 % of her body surface following ignition with inflammable liquid. She was admitted to a local hospital the same day. On the third day she was transferred to the Burn Care Centre at the Pakistan Institute of Medical Sciences in Islamabad. She was found to have deep burns on her face, neck, back, upper arms and hands.

Burns due to ignition of flammable liquids usually result in deep injuries. In full-thickness burns, where both the epidermis and the dermis have been destroyed, all necrotic tissue has to be removed surgically. The injured skin areas must then be covered with split-thickness skin grafts from areas with intact skin. In modern burn care, efforts are made to excise all necrotic tissue from areas with full-thickness damage during the first four days after the injury. This limits the possibility of necrotic tissue becoming a source of serious systemic infections. Prompt covering with skin grafts also reduces the extensive catabolic response after a burn injury and the wounds will heal more rapidly, the hospital stay will be shorter and the final cosmetic result better. Treatment of extensive burns is resource-intensive and requires close cross-disciplinary cooperation. Deep burns affecting 30–35 % of the body surface area is a life-threatening condition.

This patient had a right to (free) treatment in Norway. When contacted by the Norwegian Foreign Service on the third day after the injury, Haukeland University Hospital therefore responded that the patient could be received at its Burn Centre. Her return to Norway took time, partly because the Burn Centre in Islamabad advised against moving the patient for the first ten days. A brief report from the hospital in Islamabad described their treatment, which had included repeated debridement of the burn wounds about every four days, multiple blood transfusions, antibiotics (piperacillin-tazobactam and teicoplanin) and systemic steroids. They had not commenced skin grafting. During her hospital stay in Pakistan she was reported to have maintained spontaneous respiration and circulatory stability.

Repatriation of seriously injured persons from remote destinations is a challenge when the hospital abroad that is providing treatment indicates that the patient is not stable enough for long-distance transport. However, patients requiring intensive care during transportation can be moved over very long distances if the transfer is well organised and takes place with appropriate equipment and experienced personnel. This patient was reported to have stable circulation and respiration. With hindsight, she would probably have benefited from earlier repatriation to Norway.

On day 25 we received a message from SOS International in Copenhagen about transportation home with arrival in Bergen late in the evening of day 27.

If optimal cleaning of burn wounds is hindered due to inadequate personnel, equipment, pain relief or hygiene conditions, conditions for bacterial growth will be favourable in the affected wound areas. In 1998 we had an outbreak of infection at our Burn Centre after the transfer of a patient from a hospital in Alicante, Spain, with an *Acinetobacter baumannii* that was resistant to all available antibiotics apart from colistin (1).

We have subsequently strengthened our anti-infection procedures when receiving patients with burn injuries sustained abroad, and have thereby prevented the spread of multidrug-resistant bacteria.

Before the patient arrived, a large room had been prepared with its own entrance, own sluice room and options for all common intensive care therapies, in addition to a shower trolley. The personnel implemented contact precautions, and included in addition a face mask in accordance with the hospital's guidelines for patients transferred from abroad. On arrival in Norway in the evening of the 27th day after the injury, the patient was

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able to speak, but was tired. Her blood pressure was 145/83 mm Hg, pulse was 94/min and her temperature was 37.1 °C. Laboratory results, with normal values in parentheses, were: Hb 6.8 g/dl, leukocytes 10.3 · 10^9/l (3.5–11 · 10^9/l), CRP 263 mg/l (< 5 mg/l), creatinine 85 μmol/l (45–90 μmol/l) and albumin 17 g/l (39–49 g/l).

The patient's vital parameters were stable on her arrival. She was anaemic, and in the course of the night she received two units of erythrocyte concentrate. Her CRP level was markedly increased. In severe burns it can be difficult to distinguish a pronounced inflammatory process from a bacterial infection by means of the CRP value.

The next morning (day 28) greenish, discoloured bandages were removed. With the patient on the shower trolley and under general anaesthesia, all wound surfaces were cleaned with diluted Hibiscrub and then thoroughly rinsed. Four weeks after the injury, there were still open wound areas covering 28 % of the body surface area. The eschar had detached from most of the full-thickness wounds, and there were several large areas of thick fibrin deposits on the trunk and arms. After thorough cleaning, swab samples were taken from the wound surfaces for bacteriological testing. Samples were also taken from the nose, throat and perineum (screening for methicillin-resistant staphylococcus aureus (MRSA)), and from the anus, for multidrug-resistant enteric bacteria (including vancomycin-resistant enterococci (VRE)). All open wound surfaces were covered with Flamazine cream. A central venous catheter (CVC) inserted at the hospital in Pakistan was removed, and the tip of this catheter cultured. Bacteriological findings from samples taken the first 12–36 hours after arrival at the Burn Care Centre are summarised in Table 1.

Table 1 Bacteriological findings in samples taken after patient's arrival at Haukeland University Hospital

Location	Microbes	Resistance mechanisms
Blood cultures	*Pseudomonas aeruginosa*	AmpC/efflux/porin loss
	Klebsiella pneumoniae	$ESBL_M$ and $ESBL_{CARBA-D}$
Removed central venous catheter	*Klebsiella pneumoniae*	$ESBL_A$ and $ESBL_{CARBA-D}$
	Proteus mirabilis	$ESBL_{CARBA-B}$
	Morganella morganii	$ESBL_{CARBA-B}$ and $ESBL_{CARBA-D}$ 16S rRNA-methylase possible
	Acinetobacter baumannii	$ESBL_{CARBA-D}$
Bronchial lavage	*Klebsiella pneumoniae*	$ESBL_M$ and $ESBL_{CARBA-D}$
Wound secretion	*Klebsiella pneumoniae*	$ESBL_M$ and $ESBL_{CARBA-D}$
	Klebsiella pneumoniae	Wild type isolate
	Proteus mirabilis	$ESBL_{CARBA-B}$
	Enterobacter cloacae	$ESBL_A$
	Providencia stuartii	$ESBL_M$ and $ESBL_{CARBA-B}$
	Pseudomonas aeruginosa	$ESBL_{CARBA-B}$ 16S rRNA-methylase possible
	Pseudomonas aeruginosa	AmpC/efflux/porin loss
	Stenotropomonas maltophilia	–
	Methicillin-resistant *Staphylococcus aureus*	–
	Alkaligenes faecalis	–
	Bordetella trematum	–
Screening skin	Methicillin-resistant *Staphylococcus aureus*	–
Screening stool	Vancomycin-resistant *Enterococcus faecium*	VanA
	Escherichia coli	$ESBL_A$
	Escherichia coli	$ESBL_A$ and $ESBL_{CARBA-D}$
	Pseudomonas aeruginosa, carbapenem-resistant	Not determined

Given a reasonably stable patient and without definite signs of systemic infection, we chose, after gaining an overview of the extent of the injuries, not to continue piperacillin-tazobactam after the first 24 hours following the patient's arrival.

On day 29, the situation worsened dramatically. The patient had to be intubated because of increasing hypoxia. Intra-arterial haemodynamic monitoring (PiCCO catheter) revealed hyperdynamic circulation with intravascular hypovolaemia consistent with sepsis.

Serum procalcitonin was markedly elevated at 19.9 μg/l (< 0.10 μg/l).Growth of Gram-negative rods from the central venous catheter, removed the previous day and finding of MRSA DNA in skin samples were reported first. After consultation with an infection specialist, administration of intravenous gentamicin combined with meropenem and vancomycin was commenced. Because of high cardiac output and low peripheral resistance, efforts were made to raise her blood pressure – first through continuous infusion of norepinephrine and later also of vasopressin.

In view of the patient's anuria, increasing metabolic acidosis and rise in potassium to > 6.0 mmol/l, renal-replacement treatment was started in the form of continous veno-venous haemofiltration. During the next 12 hours the patient became severely hypoxic with P_aO_2/F_IO_2 ratio reduced to 7.8 kPa. High airway pressures were required in attempts to remove CO_2. Surgery for extensive removal of possibly infected skin areas was not considered to be feasible. Neither prone positioning nor start-up of a high-frequency respirator (oscillator) improved oxygenation. In a situation with extensive open wounds and a totally uncontrolled septic condition, ECMO therapy was not regarded as an option.

Thirty six hours after her arrival at Haukeland University Hospital, multi-organ failure set in. Despite the use of empirical broad-spec-

Table 2 A representative collectionof multidrug-resistant $ESBL_{CARBA}$-producing gram-negative isolates from the patient with specification of clinical sample material, bacterial species, resistance and resistance mechanism

Species	*Klebsiella pneumoniae*	*Klebsiella pneumoniae*	*Morganella morganii*	*Proteus mirabilis*	*Acinetobacter baumannii*	*Providencia stuartii*	*Pseudomonas aeruginosa*	*Escherichia coli*
Isolated from	Blood, lower respiratory tract, wound	Central venous catheter	Central venous catheter	Central venous catheter, wound	Central venous catheter	Wound	Wound	Rectal screening
Antibiotics[1]								
Piperacillin-tazobactam	R	R	R	R	R[3]	R	R	R
Cefotaxime	R	R	R	R	R[3]	R	R[3]	R
Ceftazidime	R	R	R	R	R[3]	R	R	R
Cefuroxime	R	R	R	R	R[3]	R	R[3]	R
Aztreonam	R	R	R	S	R[3]	I	R	R
Meropenem	R	S[2]	I	I	R	S[2]	R	S[2]
Ertapenem	R	S[2]	R	R	R[3]	S[2]	R[3]	R
Imipenem	R	S	R	R	R	R	R	S[2]
Gentamicin	R	R	R	R	R	R[3]	R	S
Amikacin	R	S	R	R	R	R	R	S
Tobramycin	R	R	R	R	S	R[3]	R	R
Ciprofloxacin	I	R	R	R	R	R	R	R
Tigecycline	I	I	R[3]	R[3]	R[3]	R[3]	R[3]	I
Trimethoprime-sulfametoxazole	S	R	R	S	R	R	R[3]	R
Phosphomycin	R	S	R	R	R[3]	R	R[3]	S
Colistin	S	S	R[3]	R[3]	S	R[3]	S	S
Resistance mechanism[4]								
$ESBL_{CARBA}$	OXA-48	OXA-48	OXA-48, NDM	NDM	OXA-23	NDM	VIM	OXA-48
$ESBL_{A}$	–	CTX-M	CTX-M	CTX-M	–	–	–	CTX-M
$ESBL_{M}$	CMY	–	–	–	–	CMY	–	CMY

[1] Categorisation of susceptible (S), intermediate (I) and resistant (R) in accordance with EUCAST's clinical breakpoints version 6.0

[2] The isolate is classified as susceptible (S) according to currently applicable clinical breakpoints, but the minimum inhibitory concentration (MIC) is higher than a wild type species without resistance mechanisms

[3] Species with inherent resistance to the antibiotic in question, or the antibiotic in question is not appropriate for treating this species

[4] β-lactamase-mediated resistance mechanism classified according to Giske et al (20)

trum antibiotics and extensive organ-support measures her condition rapidly deteriorated. The patient died in intractable septic shock only 56 hours after being transferred from Pakistan to Norway.

The first samples for microbiological testing were taken the morning after her transfer. Rapid results on microbe identity and resistance patterns are vital for targeted antibiotic therapy. Methicillin-resistant *Staphylococcus aureus* was detected directly from screening samples by means of a commercial system (GenXpert), and the results reported within three hours.

The other samples were cultured using traditional microbiological methods. The results of these tests normally take 2–3 days, and longer for mixed cultures. In this case, the microbiological diagnostic process was significantly shortened by using mass spectrometry to identify the cultured colonies and direct resistance testing of positive blood cultures. It was therefore possible to report preliminary resistance patterns with suspicion of extended spectrum betalactamase (ESBL)-producing gram negative rods on the following day. Findings of microbes and clinically significant resistance mechanisms are shown in Table 1. Carbapenemase production was detected in a total of eight different, highly multidrug-resistant Gram-negative enteric bacteria (seven different species) (see Table 2).

Gram-negative bacterial isolates suspected of carbapenemase production were forwarded for further tests at the Norwegian National Advisory Unit on Antimicrobial Resistance (K-res) at the University Hospital of North Norway, Tromsø. The results showed that the patient was colonised/infected by several different highly multidrug-resistant Gram-negative bacteria with different kinds of plasmid-mediated (transmissible) carbapenemases ($ESBL_{CARBA}$), often in combination with other ESBL types ($ESBL_A$ and $ESBL_M$), which resulted in reduced susceptibility/resistance to almost all β-lactam-antibiotics (Table 2).

The resistance profile showed that all the isolates were highly multidrug-resistant. Several of the bacteria were only susceptible to last-resort antibiotics (colistin). Further, several of the isolates were also highly resistant to gentamicin, tobramycin and amikacin, which indicates the presence of transmissible enzymes (16S rRNA methylases) which confers broad-spectrum aminoglycoside resistance (2).

Discussion

The course of the patient's illness illustrates an increasingly relevant problem: serious infections caused by multidrug-resistant bacteria acquired abroad.

Burn wounds are rapidly colonised by bacteria from the patient's own flora or from the environment. Nevertheless, bacterial growth on wound surfaces does not necessarily mean a wound infection that must be treated. More emphasis must be placed on local signs of inflammation, and particularly on microbes in samples from normally sterile areas, such as the blood, lower respiratory tract or central venous catheter in this case.

Both operations on and care of burn wounds may cause transient bacteriaemia. Figures for the frequency of transient bacteriaemia in connection with the cleaning of large burn wounds have varied from 13 % to 65 % (3, 4).

For the first twenty four hours after arrival at the Burn Centre, the patient was given piperacillin-tazobactam. An overall clinical assessment after the wound surfaces had been thoroughly cleaned did not give grounds for continuing with antibiotics. In retrospect we also know that all Gram-negative isolates from normally sterile areas proved subsequently to be resistant to piperacillin-tazobactam.

The microbiological analyses of the wound samples were very work-intensive because we found up to ten different species of bacteria. Most of the Gram-negative isolates proved to produce plasmid-mediated ESBL types ($ESBL_A$, $ESBL_{M-C}$, $ESBL_{CARBA}$). It is probable that the patient's multidrug-resistant isolates were acquired during her stay in a hospital in Pakistan. Several studies have shown that travel and hospital stays abroad, particularly in the Indian subcontinent, are risk factors for colonisation or infection with multidrug-resistant microbes (5–7). Isolation and screening of patients are important for avoiding secondary spreading. Although such isolates are rare in Norway, outbreaks secondary to $ESBL_{CARBA}$-producing isolates introduced through importation have been described (8).

There has been a steady increase in the use of carbapenems in Norway since 2006 (9). The agents are effective, with a very broad-spectrum antibacterial effect and moderate toxic adverse reactions. Studies show a clear association between liberal use of broad-spectrum antibiotics and the frequency of resistance (10–12). A study from the Burn Centre in question in Islamabad is also highly relevant, as it showed that in 2012 24 % of *K. pneumoniae* isolates and no less than 36 % of *P. aeruginosa* isolates in burn patients in Islamabad were resistant to imipenem (13).

There are clear Norwegian guidelines for screening for possible MRSA infection/colonisation of patients who have been admitted to hospitals outside the Nordic countries (14). Our experience indicates that the same level of focus must be on determining whether patients transferred from abroad are infected, or colonised, with multidrug-resistant Gram-negative rod bacteria or VRE. New recommendations from the Norwegian Institute of Public Health recommend that all patients who have been in health institutions outside the Nordic countries be tested for ESBL-producing bacteria if they are later admitted to Norwegian hospitals (15).

Rapid microbiological diagnostics and targeted treatment are crucial for effective treatment of serious systemic infections caused by multidrug-resistant bacteria. In the present case, new methods such as mass spectrometry, direct resistance testing and gene technology methods permitted faster results for methicillin-resistant *Staphylococcus aureus* and suspicion of ESBL-producing Gram-negative bacilli.

The incidence of methicillin-resistant *Staphylococcus aureus*, linezolid- and/or vancomycin-resistant enterococci and Gram-negative rod bacteria with detected carbapenemases ($ESBL_{CARBA}$) is monitored through the Norwegian Surveillance System for Communicable Diseases (MSIS) for public health reasons. $ESBL_{CARBA}$, also called carbapenemases, are β-lactamases that can deactivate carbapenems in addition to other β-lactams (16). Isolates with $ESBL_{CARBA}$ are rare in Norway (9), but rapidly increasing worldwide. The global spread of enteric $ESBL_{CARBA}$ -producing Gram-negative bacteria gives grounds for particular concern because of multidrug-resistance with very few or no effective treatment options.

Several $ESBL_{CARBA}$-positive isolates were also resistant to aminoglycosides and fluoroquinolones. This combination provides broad-spectrum resistance to the antibiotics groups that are most important in our treatment of severe bacterial infections. The genes that code for these resistance mechanisms are mainly located on mobile DNA elements that can easily be transferred between different species of bacteria. This results in more effective dissemination of resistance in a bacterial population in particular under antibiotic selection.

The choice of antimicrobial therapy under such circumstances is very difficult and experimental. There are currently ongoing but not yet available randomised clinical trials to provide an evidence-based therapy option (16, 17). Summaries from a number of observational studies support the choice of combination therapy rather than monotherapy for multidrug-resistant $ESBL_{CARBA}$-producing *Enterobacteriaceae* (17, 18). Meropenem/doripenem and colistin should be included in these therapies. In addition, an aminoglycoside, tigecycline, phosphomycin or rifampicin can be added, depending on resistance patterns. Tängden and Giske (16) recommend a combination of colistin and meropenem if the minimum inhibitory concentration (MIC) for carbapenem is ≤ 4 mg/l. If MIC for carbapenem is > 8 mg/l or for empirical treatment of suspected $ESBL_{CARBA}$ sepsis without known resistance, three agents should be chosen by adding tigecycline to colistin and meropenem. Due to a frequent link between aminoglycoside and carbapenem resistance, aminoglycosides are a doubtful choice as a third agent. Colistin as monotherapy is not recommended because of the high risk of therapy failure (16).

When transferring patients after extensive hospital treatment abroad, routine consultation with infection control personnel is recommended. Patients must be isolated on arrival at a hospital in Norway. It is a matter for discussion whether the isolation routines should be maintained in certain cases even if screening tests for MRSA and other resistant bacteria are negative, particularly because ongoing antibiotic therapy during sampling may result in false-negative test results. This applies particularly if a patient has a wound with secretion, has had intensive care treatment, has been treated for burn injuries or undergone surgery abroad.

More than a year after the patient's death, we have not re-encountered any of the multidrug-resistant isolates in clinical isolates

from patients who have subsequently been treated in the department.

Conclusion

Patients who are transferred from hospitals abroad may be infected or colonised with highly multidrug-resistant Gram-negative rod bacteria in addition to MRSA and VRE. The handling of these patients should therefore be planned before the patient arrives.

Good communication between clinicians, microbiologists and infection control personnel is important. Fast microbiological diagnostics with rapid identification of the need for customised antibiotic treatment may be crucial.

In the event of septic shock it is very important to start effective antimicrobial therapy as soon as possible (19). With Gram-negative septic shock it is advisable to provide empirical coverage with two bactericidal antibiotics that cover *Pseudomonas*, for example meropenem and gentamicin. However, as $ESBL_{CARBA}$ resistance is often linked to resistance to aminoglycosides, even this combination may involve a risk of therapy failure. In such cases it will be necessary to include colistin and tigecycline in the therapy regimen until the resistance pattern permits a transition to less nephrotoxic agents.

The patient's family have consented to the publication of the article.

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