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RESEARCH ARTICLE

INFECTIONS BY OXA-48-PRODUCING ENTEROBACTERIACEAE IN SEVERE BURN PATIENTS: CASE REPORT AND LITERATURE REVIEW

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Abstract

Burn patients admitted to intensive care units (ICUs) are particularly vulnerable to infections, which are the leading cause of death, whether bacterial or fungal. Prognosis is further compromised when the causative pathogens are multidrug-resistant bacteria, a growing global threat that limits therapeutic options, especially due to the lack of progress in the development of new antibiotics. Among these pathogens, carbapenemase-producing Enterobacteriaceae (CPE), particularly those producing the OXA-48 enzyme, are a leading cause of both community-acquired and nosocomial infections, with OXA-48 being the most prevalent carbapenemase gene in Morocco. We report the case of a 12-year-old child admitted for severe thermal burns who developed colonization by carbapenemase-producing Enterobacter aerogenes (OXA-48) during hospitalization. Based on this case and a review of the literature, we discuss the profile of healthcare-associated infections in severe burn patients, the diagnosis, and the therapeutic management of infections caused by CPE.

Introduction:-

A burn is considered severe when it affects more than 20% of the total body surface area (TBSA), leading to disruption of vital functions. (1) Advances in burn resuscitation have significantly improved survival rates for burn patients, whose injuries were fatal just a few decades ago. However, new therapeutic challenges have emerged. Infections, especially healthcare-associated infections (HAIs), have become the leading complication following burns. Sepsis remains the primary cause of death among both adult and pediatric burn patients.

Microbiological analysis of infections in burn patients reveals increasingly alarming rates of multidrug-resistant bacteria. This global epidemiological threat complicates the therapeutic management of burn patients, requiring multidisciplinary collaboration to optimize the care of these complex cases.

We present the case of a 12-year-old child admitted for severe thermal burns, during which local swabs revealed colonization by Enterobacter aerogenes (OXA-48), complicated by sepsis of cutaneous origin.

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Observation:-

H.M., a 12-year-old child with no notable medical history, was the sole survivor of a bus accident in which the vehicle caught fire, leaving 36 victims.

Upon admission, the patient was conscious and hemodynamically stable, weighing 24.2 kg and standing at 150 cm, with a body mass index (BMI) of 11 kg/m². Third-degree deep thermal burns were noted on the scalp, back, and upper and lower limbs. The burned skin area (BSA) measured 5,300 cm², corresponding to 50% of the total body surface area (10,525 cm²).

Initially, the patient was treated at Guelmim Hospital in southern Morocco, where daily dressing changes were performed, along with decompression incisions on the dorsal aspect of both hands and a thin skin graft on the right hand's dorsal side. Four months post-admission, the patient developed severe malnutrition, cachexia, and inflammatory anemia (hemoglobin 6.5 g/dL, CRP 80 mg/L, blood urea 0.06 g/L), leading to graft failure on the right hand.

Given the need for specialized care, the patient was transferred to the Burn Unit at Mohamed V Military Hospital in Rabat.

General Management:

1. **Blood transfusion:** Four leukocyte-depleted erythrocyte concentrates were administered, raising hemoglobin to 11 g/dL.
2. **Enteral nutrition:** Early nasogastric tube feeding was initiated to correct malnutrition, targeting 2,000 daily calories using the Toronto formula. The feeding was gradually increased: 1,000 calories for two days, then 1,500 calories, and finally 2,000 calories, supplemented with trace elements.
3. **Microbiological sampling:** Multisite microbiological swabs were taken upon admission to guide antibiotic therapy. Key pathogens identified included Staphylococcus aureus (methicillin-sensitive), wild-type Pseudomonas aeruginosa, Proteus mirabilis, and Providencia stuartii.
4. **Pain management:** Opioids were used for analgesia.

Local Management:

Daily greasy dressing changes were performed under general anesthesia for two weeks in the operating room. Bleach-based hydrotherapy was conducted daily, followed by rinsing and greasy dressing application.

Fifteen days after admission, an autograft was performed on the scalp but later complicated by graft loss due to infection. As advanced coverage techniques (e.g., sandwich allografts, Humeca) were unavailable, the patient was transferred to the Percy Army Training Hospital Burn Treatment Center in France, where multiple surgical interventions were carried out.

At this stage, the patient underwent several successive surgical interventions, including:

1. Autograft from the back using a thin epidermal harvest from the thighs, combined with a xenograft sandwich technique.
2. Excision and autograft on the postero-lateral aspect of the right upper limb using the Meek technique.
3. Scalp autograft surrounding an occipital defect, with exposure of approximately 50 cm² of bone.
4. Excision of the external table of the occipital bone, followed by negative pressure therapy (VAC).
5. Full-thickness skin autografts to the forehead, temple, and right cheek.

At day 11 of hospitalization at HIA Percy, local samples revealed colonization/infection by Pseudomonas aeruginosa(sensitive) and Enterobacter aerogenes (OXA-48), a carbapenemase-producing Enterobacteriaceae (CPE) among highly resistant emerging bacteria. These strains, which exceeded detection thresholds in digestive carriage, emerged due to antibiotic prophylaxis associated with successive graft surgeries. These pathogens spread rapidly to all sites except the head.

Local care was adjusted to include sodium hypochlorite baths every 48 hours and Mafénide irrigation. The child developed sepsis originating from the skin, with bacteremia caused by Pseudomonas aeruginosa. After 48 hours of treatment with Ceftazidime and Gentamicin, the infection was controlled, and the patient showed clinical improvement. Antibiotic therapy continued for 15 days.

The child remained in strict isolation to prevent cross-contamination. Enteral nutrition was maintained continuously, leading to weight gain and improved appetite. The patient was transferred for continued rehabilitation after three months.

Discussion:-

Burn patients admitted to intensive care units are particularly vulnerable to infection, the leading cause of death, whether bacterial or fungal. According to the French Society for the Study and Treatment of Burns (SFETB), 19% of burn center patients experience at least one infection, a figure that rises to 48% among those with burns covering more than 30% of their body【1】.

Infections in burn patients often follow a predictable timeline. Skin and soft tissue infections emerge early during hospitalization, typically within the first week, while pneumonias, bacteremias, and urinary tract infections develop later, with an average onset of 30 days post-admission【2】.

Microbiological Profile and Challenges:

Burn wound microbiology evolves significantly over time. Each institution and hospitalization phase presents varying pathogen spectra. Intensive care unit stays increase the risk of acquiring carbapenemase-producing Enterobacteriaceae (CPE). Colonization often extends beyond the skin to other body sites【3】【4】.

Carbapenemase-producing Enterobacteriaceae (CPE), particularly OXA-48 producers, pose major challenges due to therapeutic difficulties, potential horizontal gene transmission, and hospital outbreak risks【4】【5】. Since their first identification in Turkey (2001), OXA-48 producers have spread globally. Diagnosing OXA-48 CPE remains challenging due to their low carbapenem hydrolysis efficiency. Thus, combined phenotypic and genotypic tests are recommended for accurate identification【5】.

Although it is a carbapenemase, the microbiological diagnosis of OXA 48-producing Enterobacteriaceae (EPC) remains difficult. Indeed, OXA 48 has a relatively weak hydrolytic capacity for carbapenems; consequently, the use of phenotypic methods alone can lead to false negatives. OXA 48-producing isolates appear sensitive to carbapenems while patients do not improve under carbapenem treatment. Therefore, a two-step approach is recommended, namely a screening process followed by a phenotypic or genotypic confirmation test to detect the presence of carbapenemase. [5]

The best therapeutic approach for managing infections caused by OXA-48-producing Enterobacteriaceae remains controversial. Clinical situations requiring systemic antibiotic therapy primarily concern severe infections, potentially bacteremic, and associated with high morbidity (4,6). The choice of appropriate treatment should be made on a case-by-case basis, balancing efficacy and toxicity, while considering the regimens proposed and recommended in the literature.

Most OXA-48-producing Enterobacteriaceae exhibit a multidrug-resistant phenotype that severely limits therapeutic options. This multidrug resistance is often due to the combination of carbapenemases and extended-spectrum beta-lactamases (ESBLs). The main drugs used to treat EPC include beta-lactams (carbapenems, ceftazidime, and aztreonam), polymyxins (colistin, polymyxin B), aminoglycosides, tigecycline, and fosfomycin. It is important to note that most of the available studies are retrospective studies involving a limited number of patients, while no randomized controlled trials are yet available. [7]

Theoretically, cephalosporins such as ceftazidime can be used for OXA-48-producing isolates in the absence of co-production of ESBLs, as these drugs are weakly or not hydrolyzed by these enzymes. Mimoz et al. [8] developed an experimental model of peritonitis induced in mice using an ESBL-negative OXA-48-producing Klebsiella pneumoniae strain. Clinically, Levast et al. reported a case of neonatal pulmonary infection caused by an ESBL-negative, OXA-48-producing Klebsiella pneumoniae successfully treated with a combination of cefotaxime and amikacin, which is consistent with the results of Mimoz et al. [8]

As for carbapenems, varying levels of hydrolysis have been reported. Imipenem and doripenem, despite being sensitive in the study by Wiskirchen et al., showed low efficacy in the in vivo mouse model, while ertapenem's activity was weak both in vitro and in vivo [8]. This was also the case in the study by Lutgring et al., where all isolates recovered from patients between 2010 and 2014 were resistant to ertapenem. [9] Clinically, the use of carbapenems as monotherapy resulted in cure and survival rates ranging from 0% to 66% [9-10]. In most cases, these were bacteremias complicating the placement of intravenous catheters. Thus, carbapenem treatment failure is probably more significant, as many therapeutic successes have been attributed to the removal of infected central

venous catheters.
Polymyxins, namely colistin, have become the main agent in the treatment of EPC, typically in combination with other antibiotics. [11] However, the use of colistin should be limited to documented infections with Gram-negative bacteria (GNB), defined as sensitive, when no other options are available. [6] Tzouvelekis et al. reported disappointing results among patients treated with colistin as monotherapy (47.2% therapeutic failures). [12] When colistin was combined with tigecycline or an aminoglycoside, this therapeutic failure rate decreased to 32%. Even better, when colistin was combined with a carbapenem, the therapeutic failure rate dropped to 5%. In addition to its renal toxicity, it is difficult to manage because, as a prodrug, it has low and delayed bioavailability, while its pharmacodynamic profile is concentration-dependent bactericidal. Aminoglycosides can be considered the drugs of choice to integrate into the therapeutic regimen for EPC infections. Moreover, this aminoglycoside-carbapenem combination appears to be the most effective for treating EPC infections. [12]
Tigecycline is usually active in vitro against GNB (including multidrug-resistant strains), except for **P. aeruginosa** and **Proteus**. [13] However, therapeutic failures have been reported when the minimum inhibitory concentration (MIC) is ≥1 mg/l. Consequently, the FDA recommends avoiding prescribing tigecycline as monotherapy for severe infections. However, tigecycline has proven useful when used in combination in EPC infections. [14] Finally, non-antibiotic therapies have been studied for treating osteomyelitis in a diabetic foot caused by an OXA-48-producing Klebsiella pneumoniae acquired in Tunisia, which was successfully treated with hyperbaric oxygen therapy alone. [138] Overall, these reports highlight the variability and unpredictability of appropriate therapeutic options for this type of infection.

Conclusion:-

Therapeutic management of OXA-48-producing Enterobacteriaceae infections remains subject to divergence and is not yet standardized. Managing OXA-48-producing Enterobacteriaceae infections requires a case-by-case approach, balancing efficacy and toxicity. Prevention strategies, including regular screening for colonization and strict hygiene protocols, are essential to limit horizontal transmission. Given the growing threat of antibiotic resistance, optimizing antibiotic use and limiting unnecessary prescriptions are critical to controlling these infections. Prevention is a key aspect of management. Indeed, a regular screening protocol for colonization upon admission could help detect the appearance of EPC, isolation, strict adherence to contact hygiene measures, in addition to standard measures, in case of a positive EPC diagnostic test, are crucial steps to control horizontal transmission. According to the World Health Organization (WHO), we could soon enter a "post-antibiotic era." Therefore, preserving the few remaining drugs effective against these pathogens and, more generally, limiting the use of antibiotics and optimizing their dosages and administration methods are indisputable imperatives.

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