PAN-ANTIBIOTIC RESISTANCE AND NOSOCOMIAL INFECTION IN BURN PATIENTS: THERAPEUTIC CHOICES AND MEDICO-LEGAL PROBLEMS IN ITALY*

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SUMMARY. Many successes have been achieved in the care and treatment of burn patients in recent years, with a significant improvement in outcome. Sepsis and related problems are the major cause of death in these patients and represent an outstanding problem, also in view of the emergence of polyantibiotic-resistant germs. With regard to gram-positive organisms, the identification of methicillin-resistant Enterococci and Staphylococci does not constitute an insoluble problem, given the sustained sensitivity to glycopeptides (vancomycin, teicoplanin). More problems occur with gram-negative germs: in recent years the isolation in burn units of polyresistant Pseudomonas aeruginosa, Stenotrophomonas maltophilia, and Acinetobacter baumanii has become more frequent. In some cases, an in vitro resistance to all antibiotics tested has been observed. In these cases, the difficulty of deciding on appropriate therapy has led us to consult an infectivologist. In this article, together with our approach to these pan-resistant infections, we wish to consider the medicolegal aspect of the problem, underlining the fact that at all clinics involved in burn treatment frequently have to take important decisions regarding strategies against polyantibiotic-resistant germs. These strategies have not yet been standardized either by infectivologists or by medicolegal physicians.

Introduction

Advances in technical expertise and the knowledge of physiopathology have permitted a significant improvement in the survival and quality of life of burn patients. However, despite this progress, infection still represents a major problem that has not been completely solved.

Burns cause the destruction of the dermo-epidermal barrier, facilitating bacterial contamination, and burned tissues, in third-degree burns, are a good culture medium from where germs can reach the bloodstream and generate systemic infection. The life-saving aids (endotracheal tubes, ventilation supports, endovascular and urethral catheters, surgical drainage) used in the treatment of burn patients open up other ways of access for micro-organisms, multiplying colonization by nosocomial germs and increasing the vulnerability to infection.

In the acute phase, burn patients are also subject to important immunosuppression, which makes them more receptive to bacterial colonization and infection. This has been the rationale for immunoglobulin administration, aimed at increasing resistance to infection, but the results are still being evaluated. With the progress that has been made in resuscitation, renal failure has become rarer, and sepsis and related problems are now the major cause of death in burn patients.

Today the best control of sepsis is prevention: this can be achieved by early excision of necrotic tissues, plus correct nutritional therapy and environmental control. However, when the clinical signs of sepsis are present, adequate antibiotic therapy is necessary.

Early surgery, with the removal of necrotic tissue and the prevention of the possibility of bacterial colonization, has been shown to reduce the incidence of infection.

Other strategies involve nutritional therapy, which can improve the immune system (RNA, s3 and s6 fatty acids, arginine), and nonspecific immunostimulants such as glucan and glutamine.

Antibiotic therapy is based on the antibiograms of isolated germs in haemocultures, bronchial secretions, tampons, and urocultures, while prophylaxis in burn patients is not uniformly accepted.

To prevent epidemic diffusion of polyresistant germs, it is necessary to have adequate environmental control. The patients are placed in individual rooms with functional ventilation in order to ensure
constant air circulation and filtration. Recent studies have demonstrated that furniture is often contaminated and can be an important source of infection. The medical and nursing staff can also be responsible for cross-contamination between patients simply by moving from one room to another - they are an involuntary vehicle for germs. Clinical trials demonstrate that hand washing can decrease the incidence of nosocomial infections by 30%, and good hygienic and environmental control can prevent the diffusion and the development of multiresistant germs notwithstanding the intrinsic difficulties of respecting all the rules.

With regard to invasive devices, prevention of infection is achieved by constant replacements, in an attempt to decrease the possibility of colonization. Scientific research is working on the development of new materials for endovascular catheters and tracheal tubes that do not permit bacterial adhesion, thus decreasing the risk of contamination.

Pan-antibiotic resistance: How should it be treated?

The indiscriminate use of empiric antibiotic therapy leads to the development of polyantibiotic-resistant germs. The growth has been reported of multiresistant Pseudomonas aeruginosa and Acinetobacter baumannii in patients subjected to prolonged antibiotic therapy. This is particularly important in burn units and intensive care units, where the incidence of such infections is two to five times higher than in other departments.

The development of antibiotic resistance is due to three main causes: the acquisition of new genes, Darwinian selection of resistant clones, and the natural growth of resistant germs.

With the increased frequency of infection by these multiresistant germs, antibiotic therapy has become more difficult and, in some cases, virtually impossible. For this reason, prevention takes on great importance. Prevention can be achieved by the rational use of antibiotics and the observation of hygiene rules that prevent interpersonal diffusion. When prevention fails, infection by these germs is treated with the pharmacological protocol used in neutropaenic patients; they are the paradigm of the loss of defences and infection is an absolute indication for two high-dosage antibiotic associations. The advantages of this therapy are its wide spectrum and the synergism between molecules; however, there is a higher incidence of collateral effects (nephro-oto-hepatopathy) that require strict control of plasma levels.

In the literature there is no agreement on the choice of antibiotics: some researchers recommend the association of β-lactamine and aminoglycosides, others support the use of new wide-range antibiotics such as carbapenems and third-generation cephalosporins, others regard polymyxin and colistin as the best choice, and a few others consider the association of three antibiotics (aminoglycosides, fluorchinolones, and third-generation cephalosporins) to be more effective.

An analysis of the literature produces no evidence of significant differences between the use of two synergetic antibiotics and monotherapy with a wide-range antibiotic, while there is increased interest in new molecules such as fourth-generation cephalosporins.

It must however be stressed that studies of therapeutic possibilities in pan-resistant infections are often not controlled, and this makes the choice of antibiotics more difficult.

Poly-antibiotic resistance in burn patients

In our experience in recent years, we have seen a significant increase in the number of isolations of meticillin-resistant staphylococci, poly-resistant gram-negatives, and Acinetobacter and Pseudomonas resistant to all antibiotics tested.

With regard to gram-plus, the most frequently isolated germs have been staphylococci (Aureus, Epidermidis, etc.). To begin with, these germs were brought in from the external environment and were sensitive to the most commonly used antibiotics, but during the patients’ hospital stay we saw a progressive increase in antibiotic resistance, ranging from penicillin/methicillin resistance to poly-resistance, with sensitivity being maintained only to glycopeptides (vancomycin and teicoplanin). In some cases poly-antibiotic-resistant germs were isolated on admission. In burn patients the growth of meticillin-resistant germs is quite common (50%), frequently in association with gentamicin-resistance (30%) and ciprofloxacin-resistance (35%). This leads to the use of more dangerous antibiotics, such as vancomycin or teicoplanin, only after identification and an antibiogram.

The problem is more complex in the case of gram-minus. Germs like Acinetobacter, Stenotrophomonas, and Pseudomonas are frequently involved in nosocomial infections with the common development of antibiotic resistance. In recent years we identified in our patients a clone of Acinetobacter, isolated from...
different patients in various sites (haemocultures, 40%; endovascular catheters, 29%; swabs, 20%; bronchial secretions; 6%; urocultures, 5%). This continued with an increasing trend until January 1999, when all five patients then in the Burn Unit were infected by this germ. In the beginning the germ was “good” with poly-antibiotic sensibility, but after a year it progressively became pan-resistant. This appeared to follow therapy with various molecules (Piperacillin, Amikacin, Imipenem, Cilastatin).

Our approach, after isolation of a pan-resistant germ, depended on the patient’s clinical condition and, in particular, on the presence of sepsis diagnosed (following the guidelines proposed by the Consensus Conference of the American College of Chest Physicians and the Society of Critical Care Medicine in 1991) on the basis of the presence at least of two of the following clinical signs:

* temperature > 38 °C or < 36 °C
* heart rate > 90
* respiration > 20 or PaCO₂ < 32
* WBC > 12,000 or < 4000, or immature cells > 10%.

We first of all reinforced our isolation and disinfection protocols. Environment controls on washbasins, beds, and hydrotherapy rooms revealed Acinetobacter baumannii and Pseudomonas aeruginosa colonization, confirming that environmental contamination was a potential source of nosocomial bacteria transmission. These ambient reservoirs could explain the difficulty of eradicating bacteria that were isolated in some already pan-resistant cases in new patients, after a silent period.

With regard to therapy, in patients with no signs of sepsis we did not use any antibiotics. We put the patient’s clinical condition and, in particular, on the presence of sepsis diagnosed (following the guidelines proposed by the Consensus Conference of the American College of Chest Physicians and the Society of Critical Care Medicine in 1991) on the basis of the presence at least of two of the following clinical signs:

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Medico-legal aspects

The great difficulties of medico-surgical activity, together with the evolution of jurisprudence, have led to an increase in legal procedures, with the ever-present risk of physicians being called upon to answer in penal and civil courts for damage deriving from a clinic’s professional activity. There is thus a conflict between two common interests: on the one hand, the work of the clinic, whose target is the health of the patient and, on the other, the normal human desire to enjoy “good health”.

In the event of injuries to a patient deriving from the work of a professional, these two interests inevitably diverge and lead to the very likely possibility that the patient takes the clinic to court for the damage done, or that the patient demands compensation for civil damages. This leads to a penal and/or civil case with new medico-legal problems in terms of responsibility that are difficult to resolve.

It is natural for a clinic involved in such delicate clinical therapy to consider the legal consequences of possible failure, since in actual fact one has to use therapeutic strategies that are not yet standardized in cases of poly-antibiotic-resistant or pan-resistant micro-organisms.

Analysing the problem from the medico-legal point of view, the juridical relation between the hospital clinic and the patient has first of all to be examined; the elements of possible professional liability related to the behaviour of the clinic itself also have to be evaluated.

The civil responsibility that a hospital clinic may incur during fulfilment of its duties in the hospital that has engaged the physician for the performance of the treatment given to the patient is usually a question of contract. This contract is regulated by Article 2230 et seqq. of the Italian Civil Code (ICC). Default can cause damage recoupable according to Article 1218 of the ICC, which defines the contractual tort attributable to persons failing to observe established rules, rules that they should have conscientiously followed (default of the debtor’s obligation).

It is only right that the work of a clinic should no longer be considered beyond reproach and unobjectionable when its behaviour does not conform to standard rules of the art and causes the patient injurious after-effects for which it can be prosecut ed. After ascertainment of the causes of the injurious medical outcome, the second important element in order to define the clinic’s “professional responsibility” is to examine the notion of fault. During the juridical evaluation, this is considered to be a consequence of several behaviours, due to negligence, imprudence, and lack of skill. Lack of diligence is the result of superficial and careless behaviour, whereas lack of skill is the result of defective behaviour com-
pared with that to be expected, in the same situation, from a professional of the same “intellectual” level.31

For an indemnity to be paid, it is necessary to demonstrate the fault of the clinic, and it must be stressed that this fault is not proved by the lack of positive results but by lack of effort during the patient’s treatment: the obligation is not related to the positive outcome which, though desirable, has not been obtained. It is therefore not possible to consider the clinic responsible for the patient’s non-recovery, while it is possible to consider it responsible for not carrying out all the procedures that medical science has at disposal in such cases, regardless of the injurious effects on the patient’s physical and/or mental integrity, which would justify a case for extra-contractual indemnity. We can therefore affirm that all contractual obligations are fulfilled when the clinic uses all the techniques appropriate and necessary to treat the patient.32

The legislators have also ruled that, according to Article 2236 of the ICC, an employee’s responsibility for incompetence, and not for negligence or imprudence, can consist only in the event of serious wilfulness or default, or when the case in question is particularly complex because it has not been previously sufficiently experienced or examined, or because the therapeutic techniques are still a matter of discussion,33 or if the case has “characteristics of extraordinariness or exceptionality and has not been duly examined by science or experimented”.34 This article of the law is not enforceable in what are considered “easy or routinely executed” operations, namely those that “do not require any special skill, standard professional training being sufficient, with a minimum risk of a negative or harmful result”,35 in which cases, if “the result of the operation is a deterioration, i.e. the conditions of the patient are worsened compared with his previous condition, there is a presumption of inadequate or negligent performance of professional services.”36

It therefore follows that there is no civil liability if the clinic has used all available techniques and scientific knowledge in relation to the medical treatment of the case. Liability exists if the error is due to ignorance of basic scientific standards that cannot be called into question.

A clinic’s penal responsibility is related to the death or personal injury of the patient during the performance of diagnostic and/or therapeutic activity, i.e. offences covered by penal law.37

Penal responsibility for professional incompetence is the form most directly related to the activity of the clinic itself and, as for civil responsibility, requires that the work of the clinic has been vitiated by negligent, imprudent, or incompetent behaviour.

However, a clinic’s penal responsibility for professional liability due to incompetence, and not negligence or imprudence, has been the subject of conflicting judgements by the Italian Court of Cassation. One tendency is that the clinic has to answer for serious intentionality or liability when the medical treatment involves very difficult technical problems, in accordance with Article 2236 of the ICC;38-40 another stricter tendency holds that the enforcement of this ruling cannot be performed on the basis of analogical construction, so that the clinic will have to answer in any case for the work it has done, even for slight faults.41-43

That said, it is universally acknowledged that a good reference parameter for the evaluation of a clinic’s behaviour consists of the “medical protocols” or “guidelines” elaborated by the medical and scientific community.37 These are the standards for assessing whether a clinic has abandoned the consolidated principles of its art. However, in most cases, such protocols do not enjoy the “gift of immutability” - they are constantly being modified in the light of new problems arising in the boundless field of medicine. Clearly, these protocols cannot fill gaps that exist due to the lack of official interpretations by medical science: they are no longer a valid guide but little more than an obsolete parameter from which a clinic necessarily has to depart in order to follow other, as yet unstandardized, therapeutic paths that are still being examined by the medical and scientific community.

The clinical section of this paper presents some emblematic cases of the difficulty of managing infections caused by antibiotic-resistant micro-organisms found in the Department of Plastic Surgery of the Burns Unit in Turin CTO Hospital, and also in some other Intensive Care Units.

These infections, together with the patient’s often already compromised general condition, compound an explosive mixture that can lead to therapeutic failure, even if the most up-to-date and authoritative scientific knowledge has been followed.

In the face of such evidence, can a clinic be held responsible for mistakes and be held civilly and penal prosecutable for an alleged technical error that vitiates its professional behaviour, if the therapy has a negative result?

In the light of the above considerations, we are dealing here with a “medical service that involves the solution of very difficult technical problems” (Ar-
article 2236 ICC) by a professional physician who, in the execution of medical therapy, does not lack conscientiousness or appropriate training regarding the case he has been given, and who, during the diagnosis, therapy, and isolation of critical patients, has acted in conformity with the literature on this specific circumstance, without the possibility of following a predetermined therapeutic protocol, since the problem of the treatment of hospital infections from multiresistant micro-organisms is still today a matter of discussion and close investigation, and therefore constantly changing.

We believe that in this specific situation the failure is a clear error scientiae. We are dealing with unsolved scientific problems that may cause unavoidable error - if we can consider it an error - due to incomplete knowledge of the problem. In some cases there is no efficacious and univocal method of treatment and with the treatment now available therapeutic success is not certain. It is reasonable to recognize that in such circumstances the clinic’s behaviour is not vitiated by technical error, which is inadmissible or inexcusable, but answers to the obligation of providing all due means, as respected by the clinic in the performance of its medical service.

**Conclusions**

Control of infection is one of the most important goals in the treatment and care of burn patients. The evolution of techniques and physiopathological knowledge has permitted a significant improvement in the survival and quality of life of burn patients, but infection still represents the major cause of death. Antibiotics enable us to treat commonest infections, but we are seeing a progressive development of new multiresistant bacterial clones. These super-selected gems colonize the furniture and are difficult to eradicate.

Pending the development of new therapeutic possibilities (new antibiotics, immunomodulators, etc.) to resolve these problems, a correct approach to infections by pan-resistant germ must be based on:
* the strict application of prophylactic rules to prevent interpersonal transmission;
* the creation of precise environmental hygienic protocols;
* control of potential vehicles (operators), particularly numerous in Intensive Care Unit; and
* collaboration with infectivologists.

From the medical and legal point of view, we believe that in penal and civil law it is necessary to bear in mind the technical difficulties involved in the solution of certain clinical cases and to regard a clinic as responsible only if it has acted with serious incompetence or with ordinary negligence or imprudence.

**RESUME.** Dans les années récentes, de grands progrès ont été obtenus dans le champ des soins et du traitement des patients brûlés, avec une amélioration significative des résultats. L’infection et les problèmes corrélés constituent la cause principale de la mort dans ces patients et représentent un grave problème, aussi considérant la manifestation toujours plus fréquente de germes qui résistent aux polyantibiotiques. Pour ce qui concerne les organismes à Gram positif, l’identification de Enterococci et Staphylococci qui résistent à la méticilline ne constitue pas un problème insoluible, vu la sensibilité persistante aux glycopeptides (vancomycine, teicoplanine). Les problèmes sont plus fréquents avec les germes à Gram négatif: dans les années récentes l’isolement dans les unités des brûlures de souches polyrésistantes de Pseudomonas aeruginosa, Stenotrophomonas maltophilia et Acinetobacter baumannii est devenue toujours plus commune. Quelquesfois on a observé une résistance in vitro à tous les antibiotiques testés. Dans ces cas, la difficulté de décider la thérapie la plus appropriée a porté les Auteurs de cette étude à consulter un infectivologiste. Outre à leur approche à ces infections polyrésistantes, les Auteurs considèrent les aspects médico-légaux du problème et soulignent le fait que toutes les cliniques intéressées au traitement des brûlures sont fréquemment obligées à prendre des décisions importantes sur les stratégies à suivre contre les germes qui résistent aux polyantibiotiques. Ces stratégies n’ont pas encore été standardisées par les infectiologistes et les médecins médico-légaux.
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