Le Infezioni in Medicina, n. 2, 112-119, 2005

Casi clinici

Case reports

Linezolid in the treatment of severe central nervous system infections resistant to recommended antimicrobial compounds

Linezolid nel trattamento di infezioni cerebrali gravi e resistenti alle terapie antimicrobiche di elezione

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INTRODUCTION

Gram-positive infections are reported with increasing frequency world-wide, especially when hospital-acquired strains are involved [1-5]. This gradually advancing trend is related to the increasing selection of antimicrobial-resistant Gram-positive strains, due to the selective pressure of recommended drug regimens, which become less and less effective [1, 6-8]. The increasing prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) is the main cause of this worrying phenomenon. In Italy, the median frequency of MRSA involves more than 40% of strains in general inpatient Divisions, with particularly elevated peaks (over 60% of resistant strains) found in Intensive Care and Surgical Units [7, 9-13].

Therapeutic options for central nervous system (CNS) infection (either parenchymal or meningeal in site) are still limited, and the prognosis remains severe, especially when Gram-positive infections are involved. Moreover, CNS enterococcal diseases usually complicate the course of chronic underlying illnesses, non-HIV-associated immunodeficiency, head trauma and complicated neurosurgery [14]. While enterococcal infection is borne by an elevated mortality when involving the CNS, although it is still encountered with a proportionally low frequency, staphylococcal disease represents a mounting problem, in terms of morbidity and mortality [15, 16]. When focusing on staphylococci, in Italy infections of nosocomial origin have to be considered as caused by methicillin-resistant strains [11, 13, 17], and multiresistance is a growing concern, as expressed by the appearance and slow diffusion of strains with a lower susceptibility, or none at all, to glycopeptides as well [6, 18, 19]. Moreover, resistant Gram-positive cocci occur with increasing frequency in the community due to the spread of hospital-acquired strains [20-25].

In this context, for the management of severe nosocomial CNS infections where the role of Gram-positive cocci is highly suspected or ascertained, sound treatment has to rely on multiresistant organisms, pending *in vitro* antimicrobial sensitivity assays.

When considering the intrinsic limit represented by the blood-brain barrier, the therapeutic efficacy of both glycopeptides in the cerebral district is limited to a 10% antibiotic transfer for teicoplanin, and ranges from 0 and 18% for vancomycin [26, 27]. The novel streptogramine association quinupristin-dalfopristin has been administered in a few experiments via ventricular drainage [28, 29]. Unfortunately, such an invasive therapeutic procedure needs a surgical shunt, which remains at risk for further microbial colonization and infection.

In order to overcome these problems, a novel oxazolidinone antibiotic (linezolid) recently be-

came available in current clinical practice: its indications may include severe bacterial CNS complications where a multi-resistant Gram-positive aetiology is suspected or confirmed. As the first available derivative of the oxazolidinone class, this molecule is indicated for the management of acute or chronic infectious disease caused by Gram-positive cocci, also resistant to beta-lactams, other traditional antimicrobial agents and glycopeptides as well [20, 30, 31]. Although staphylococci are wholly susceptible, the great majority of pneumococci and an elevated percentage of enterococci may be controlled by linezolid, as ascertained by animal models and human use. In experimental models of bacterial meningitis, cerebrospinal fluid (CSF) concentrations of linezolid reach the elevated rate of 29%, compared with serum levels [32]. In carriers of a ventricular-peritoneal shunt, in absence of meningeal inflammation, linezolid easily overcomes the blood-brain barrier, leading to a CNS penetration of around 70% [33]. According to existing CSF pharmacokinetic evidence, linezolid has been increasingly administered in enterococcal CNS infections, especially in vancomycin-resistant meningeal localizations, with favourable clinical and microbiological response [34-38].

Since linezolid became available for clinical prescription, a targeted use has been performed in patients with severe Gram-positive CNS infections, characterized by a limited or a negligible response to previous therapeutic regimens, in a limited number of chronic osteomyelitis resistant to multiple previous therapeutic attempts, and in episodes of septicaemia occurring in patients with indwelling central vascular catheters of prosthetic devices (with blood cultures showing multi-resistant Gram-positive cocci) [20, 22, 24, 25, 30, 34-39]. When focusing on CNS infection, other extremely favourable pharmacodynamic aspects have to be taken into careful account: namely, the availability of linezolid formulations for both i.v. and oral administration, with maintenance of the same dosage for the oral route (due to an exceptional 100% drug bioavailability), and the possibility of operating a sequential parenteral-oral therapy when needed, without any loss of efficacy, and of shortening admission periods, although the evidence is still anecdotal and fragmentary [39].

The aim of our presentation is to report three representative episodes of severe CNS infection (one of them has been reported in the meantime, focusing on its rare microbial aetiology) where linezolid administration, either alone or in conjunction with other antimicrobial agents, led to a very satisfactory clinical and bacteriological outcome [40].

First case

A 46-year-old male with a negligible clinical history and with a pet cat, came to our attention owing to a two-day septic-like hyperpyrexia, rapidly followed by neurological signs and symptoms. Mental confusion, cognitive dysfunction, apathy and speech abnormalities occurred in the next few hours. Magnetic resonance imaging (MRI) obtained 24 hours after hospitalization disclosed an expansive right frontal process, with a centre which is remarkably hypo-intense when weighted in T1, and hyper-intense with T2 signal, suggesting a brain abscess formation. This neoformation, after gadolinium enhancement, showed a significant pathological impregnation at the borders. A surrounding oedema with mass effect and consequent dislocation of the ventricular system also occurred. Our patient immediately underwent neurosurgical drainage of a frankly purulent abscess. Empirical treatment was immediately started with imipenem (3 g/day), amikacin (1200/day), fluconazole (600 mg/day), together with dexamethazone (12 mg/day). Cytological examination of purulent smears pointed out abundant necrotic material, and a prevalence of macrophages and neu-

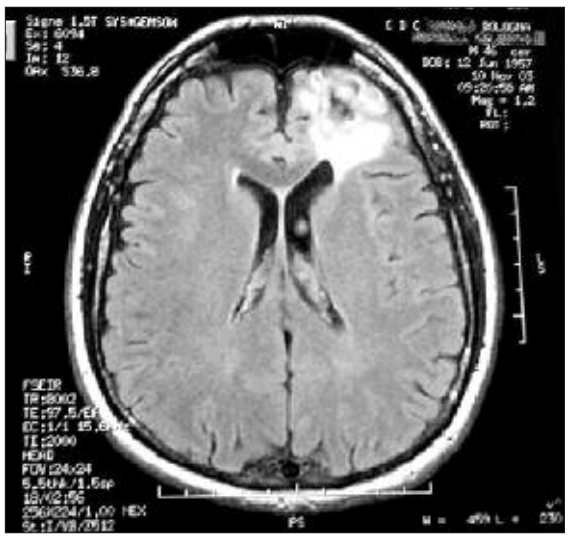


Figure 1 - MRI control of our first patient with persisting cerebral abscess, obtained immediately before linezolid introduction.

trophils, while *Capnocytophaga* spp. was cultured, and proved susceptible to all tested antimicrobial agents, save metronidazole. An endoral X-ray examination pointed out a 2.5 diameter area of mandibular bone erosion, suggesting a large granuloma. Despite susceptibility of *Capnocytophaga* spp. to *in vitro* assays and continued antibiotic treatment, a neuroradiological control carried out after three weeks showed an increased volume of frontal abscess, with concurrent reduction of brain oedema. Treatment was therefore modified, maintaining imipenem, adding vancomycin (2 g/day), and stopping amikacin. Suspected early allergic reactions to vancomycin lead to immediate drug interruption, so that i.v. linezolid (1200 mg/day) was introduced. A further MRI control carried immediately before linezolid introduction is shown in Figure 1. Concurrent surgical treatment of granulomatous mandibulary lesion was performed: biopsy examination disclosed chronic osteomyelitis, but culture examination proved negative. Finally, a whole-body scintigraphic scan with 555MBq Tc 99m HM-PAO-marked granulocytes, performed 15 weeks after neurosurgery, failed to find an increased captation in all brain areas previously affected by the extensive bacterial abscess.

Second case

A 17-year-old young male suffering from relapsing sinusitis, was admitted because of an apparent recurring left maxillary sinusitis complicated by severe homolateral headache and orbital pain, lachrymation, rhinitis and fever. Notwithstanding a negative neurological examination at hospitalization, during the subsequent days three episodes of tonic-clonic seizures affecting the left hemisoma occurred. Computerized tomography (CT) examination showed a right frontal brain abscess, and an underlying ethmoidal and right maxillar subacute sinusitis, with involvement of the homolateral lachrymal duct. A 2-week treatment was started with ceftriaxone (2 g/day), metronidazole (2 g/day), teicoplanin (400 mg/day), chloramphenicol (3 g/day), associated with dexametazone, with postponed surgical drainage. A second TC control showed a moderate improvement of neuroradiological signs, but intense leukocytosis (20,412 cells/µL) and neutrophilia (82.3%) persisted, as well as an elevated ESR rate (69, first hour). Despite full-dose 4-drug antimicrobial therapy, surgery became necessary, and both epidural empyema and cerebral abscess were drained. A further contrast-enhanced brain CT (Figure 2) evidenced a persisting, large hypodense right frontal area, with internal hypodensity, and a subtle peripheral contrast captation. A mass effect was appreciable, and frontal subdural empyema was also disclosed. Associated i.v. linezolid (1200 mg/day) and imipenem (3 g/day) was immediately started, and a significant neuroradiological and clinical improvement was rapidly achieved. A "shift" linezolid therapy was continued by oral route (at 1200 mg/day). Whole-body scintigraphy with 555MBq Tc 99m HM-PAO-marked granulocytes, carried out 7 weeks after surgery and initiation of linezolid-imipenem treatment (and subsequent follow-up with oral linezolid alone) showed no abnormal captation areas in any sites involved by the cerebral bacterial complication.

Third case

A 43-year-old female with an uneventful clinical history reported a frontal subcontinuous cephalalgia progressively worsening during the past two weeks, and not responsive to non-steroid anti-inflammatory drugs. A contrast-enhanced CT scan disclosed an extensive left

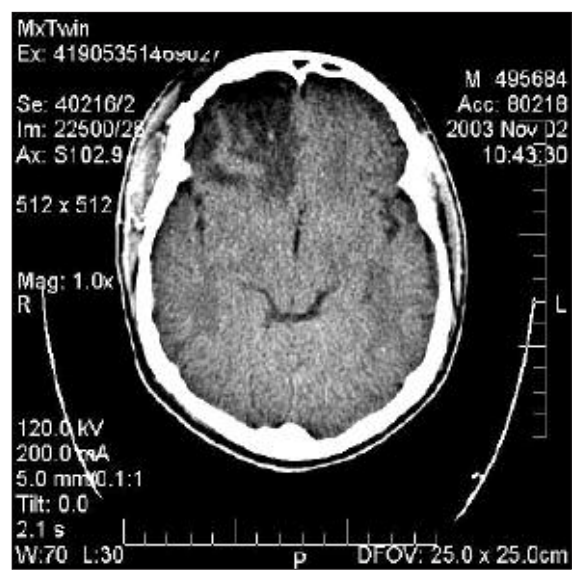
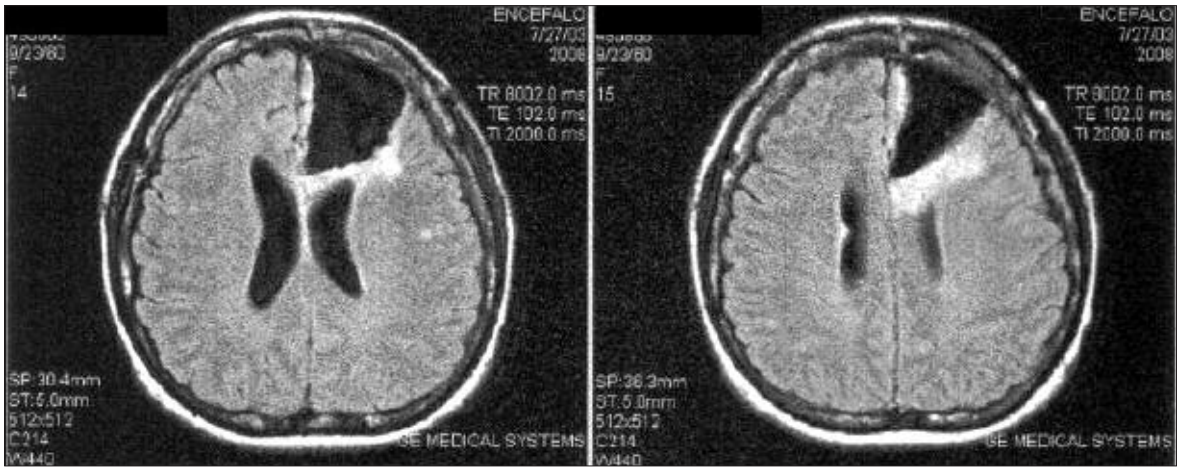


Figure 2 - Second presented patient. Before linezolid start, a contrast-enhanced computerized tomography (CT) points out a large hypodense right frontal lesion, with a hypodensity core, and a limited peripheral contrast captation. A mass effect is demonstrated, and a frontal subdural empyema was concurrent. CT examination also identified an underlying ethmoidal-right maxillar subacute sinusitis.



Figures 3a - 3b - The MRI of our third patient, obtained after neurosurgery and the first course of antibiotic treatment, shows a reduction of a residual left frontal cystic lesion, close to areas affected by the intervention. Both Figures (in particular, Figure 3b) show a great impregnation of tissues surrrounding the intervention area. On the suspicion of possible post-surgical Gram-positive bacterial meningitis, linezolid was introduced.

frontal neoplasm, complicated by oedema and mass effect on surrounding brain areas. A radical neurosurgical intervention interested a bulky cystic malignancy, partially endoventricular in site, proving to be a low-malignant oligodendoglioma under histopathological examination. Three days after the intervention a continuous-remittent fever occurred associated with a relapse of headache, and empiric ceftriaxone was started (at 2 g/daily), without apparent benefit. Repeated lumbar punctures demonstrated a pathological increase of polymorphonuclear cells (up to 80/µL), an elevated protein content (up to 134.5 mg/dL), and low glucose concentrations (43 mg/dL), in absence of microbial isolation, while leukocytosis, neutrophilia and increased ESR became apparent. Owing to the lack of improvement in the clinical-neurological picture, five days later ceftriaxone was replaced by imipenem (3 g/day), vancomycin (2 g/day) and gentamicin (160 mg/day), and there was a noticeable progressive improvement in signs and symptoms, and CSF and haematological parameters. Around 5 weeks after admission, hyperpyrexia heralded meningeal signs and a positive Laségue sign. CSF examination showed a novel increase in leukocyte count (240 cells/µL), increased protein content (57 mg/dL), and reduced glucose levels (18 mg/dL); cultural attempts remained negative. A MRI showed a reduction in a residual left frontal cystic lesion, close to areas affected by neurosurgical intervention (Figures 3a and 3b), but an evident impregnation persisted in the tissue surrounding the surgical area. At this stage, possible post-surgical bacterial meningitis due to Gram-positive organisms was suspected, and empirical treatment with i.v. linezolid immediately started, at 1200 mg/day. Our patient presented an immediate improvement in her overall clinical and neurological picture, showing complete and persistent defervescence three days after linezolid administration (Figure 4). Ten days after, CSF control tested negative, and antimicrobial therapy was interrupted, without any sequelae in the subsequent 7-month follow-up.

DISCUSSION

The recent availability of oxazolidinone and streptogramine derivatives broadens the spectrum of antimicrobial agents effective against the emerging strains of multi-resistant and glycopeptide-resistant Gram-positive cocci [1, 6, 18-20, 22, 24, 25, 30, 34-39].

The main interest in the first reported case lies in the isolation for purulent abscess material of a rare Gram-negative bacillus, belonging to *Capnocytophaga* spp. As a potential host of the oro-pharyngeal cavity of patients with impaired oral hygiene (i.e. alcoholics) and/or local inflammatory processes, as well as a common inhabitant of cat and dog oro-pharynxes [40, 41], its isolation may be explained by the

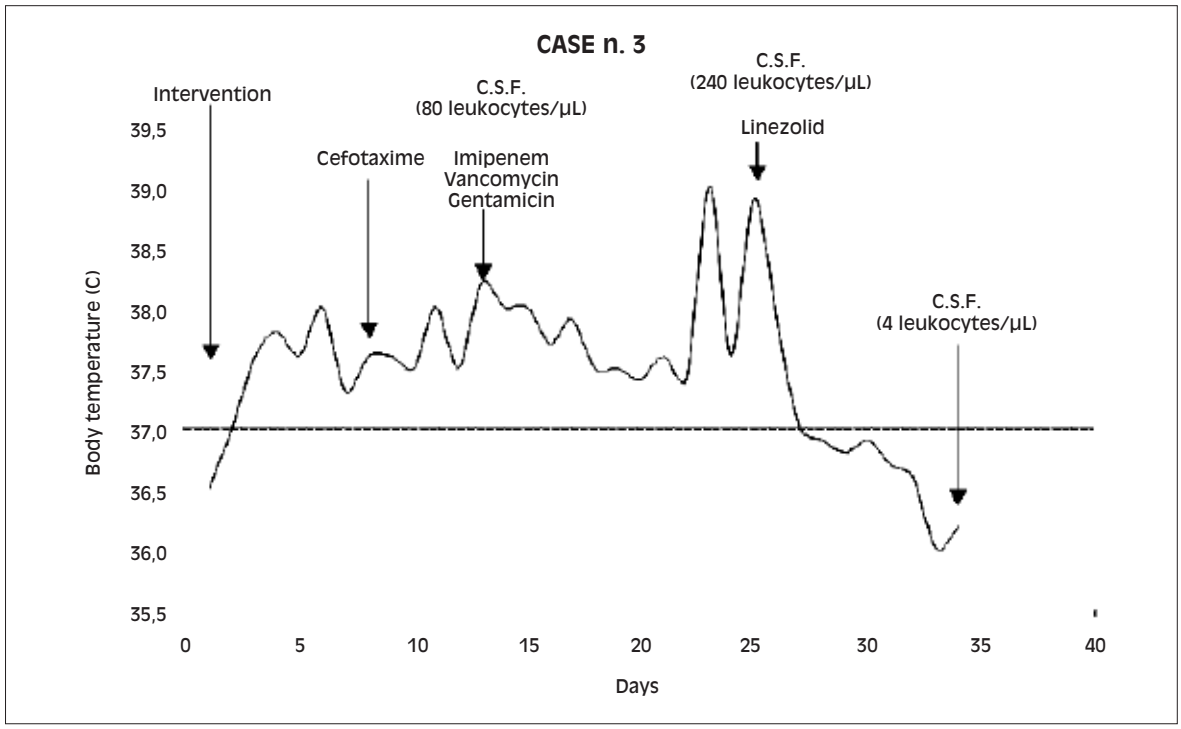


Figure 4 - Temporal profile of body temperature of our third patient, according to neurosurgery timing, and the introduction of the different antimicrobial compounds. A sustained improvement of overall clinical-neurological picture, and persisting defervescence, followed the first three days of linezolid administration.

underlying epidemiological and clinical evidence found in our patient. This microorganism, in its most common serotype *C. canimorsus* and when normoergic hosts are of concern, is a very infrequent cause of human disease, while local gangrenous lesion, or life-threatening sepsis-bacteraemia, complicated by intravascular coagulation, and kidney and liver failure, have been described in the immunocompromised host [42]. When considering the clinical course of our patient, slowly progressing CNS involvement was noticed, compared with the lightning course typically reported in immunocompromised patients. Probably the absence of an underlying immunosuppression, and combined surgical and antiobiotic treatment, prompted the clinical and microbiological success of this unusual localization of *Capnocytophaga* spp. disease [40]. Moreover, the complicated relapsing clinical-neurological course of our patient might suggest a polymicrobial infection. If the first-line treatment allowed eradication of *Capnocytophaga* spp., linezolid prompted complete resolution of cerebral abscess, which did not ameliorate after over three weeks of combined imipenem-amikacin-fluconazole administration, preceded by surgical drainage [40].

In the second case report, we could not rely on a culture isolation of examined clinical specimens, probably due to prolonged prior antimicrobial therapy which preceded neurosurgery. Just due to the need of an empirical combination, the post-operative antimicrobial therapy was conducted with linezolid (a drug specifically active against all Gram-positive cocci, and encompassing optimal penetration into cerebral tissue), and imipenem (a very broad-spectrum compound). The result proved strategically favourable, since after the improvement of the neuro-radiological picture, medical treatment was continued with oral linezolid only, after imipenem suspension, avoiding i.v. administration, and accelerating patient discharge.

With our third presented case, we underlined the clinical-therapeutic evolution of a patient who developed a post-surgical nosocomial purulent meningitis, failed to respond to a 3-drug association of vancomycin, imipenem, and gentamicin, and had a very favourable and rapid (10-day) course only after linezolid administra-

tion, in absence of relapses or sequelae. A post-surgical infection caused by multi-resistant Gram-positive agents may be strongly hypothesized, on the grounds of prior therapeutic failure, and immediate response to linezolid.

Even when based on isolated epidemiological and clinical evidence, due to the impossibility of obtaining positive cultures (which is an unavoidable limit of our experience), empiric treatment of cerebral abscess or post-surgical nosocomial infection in the setting of neurosurgery and intensive care units, could be aetiologically-related to nosocomial Gram-positive bacteria, which have an elevated rate of multiple antibiotic resistance. In this setting, even in the absence of microbial isolation often due to the predominant necrotic material obtained by either CSN biopsy or surgery, the advantages stemming from a drug like linezolid, with maintained efficacy against multiresistant Gram-positive cocci, favourable brain penetration, low toxicity profile and easy administration due to the existence of a dual route of administration, should deserve extensive, controlled studies.

In conclusion, the recently available oxazolidinone derivative linezolid represents a major advance in the treatment of CNS Gram-positive infections, especially concerning nosocomial and neurosurgery, given the unpredictable and often high prevalence of resistant organisms (including MRSA) in these high-risk settings [11, 13]. When considering the limited CSF transfer of glycopeptides and the increasing reports of resistance of Gram-positive cocci, linezolid may become the first-choice antimicrobial compound for effective, safe treatment of bacterial infections of the CNS in neurosurgical patients, and especially of metastatic cerebral abscess, and post-surgical brain infections [6, 18, 19].

Appropriate pharmacoeconomic studies have also shown that linezolid may be a favourable alternative to vancomycin [12]. This advantage is based on a lower mean admission time due to the possibility of a rapid switch from parenteral to oral route of administration, and potential anticipated hospital discharge [12]. Indeed, the 100% bioavailability of linezolid administered either i.v. or orally, allows oral administration to be introduced without changing the daily dosage.

Finally, linezolid is easier to manage than the standard glycopeptide antibiotic (i.e. vancomycin) due to a lower rate of untoward events, reduced kidney toxicity, and absence of needs to monitor plasma drug concentrations.

In conclusion, when dealing with neurosurgical infection and brain abscess, linezolid is a safe, effective choice for treating ascertained or highly suspected infections caused by Gram-positive cocci. New therapeutic scenarios are therefore open to clinicians, provided that select administration is carried out in order to preserve the drug's high potential and limit the development and spread of microbial resistance.

Key words: Linezolid, CNS, complicated infection

SUMMARY

The progressive emergence of antimicrobial-resistant Gram-positive cocci especially in the setting of surgery and intensive care, recommends particular attention in making sound therapeutic choices to overcome both microbial resistances and haematoencephalic barriers to effective local drug penetration. As in other Western countries, the occurrence of methicillin-resistant *Staphylococcus aureus* is particularly high also in Italy, especially when high-risk patients and/or settings are involved. In treating post-neurosurgical central nervous system infections (cerebral abscess and meningitis), a key issue is represented by the low cerebrospinal fluid concentration of the two available glycopeptide antibiotics (vancomycin and teicoplanin), usually recommended as first-line therapy of resistant Gram-positive cocci. Recent findings have focused on the possible role of linezolid, an oxazolidinone antibiotic, as a suitable candidate for the treatment of severe brain infection (abscesses) and post-neurosurgical infection, where treatment options and efficacy are significantly limited by the low glycopeptide transfer and the spread of glycopeptide-resistant bacterial strains. Three representative case reports (two brain abscesses and one post-surgical meningitis) are presented and discussed in light of the current literature: in all these cases, salvage linezolid treatment proved resolutory.

RIASSUNTO

Il progressivo emergere di cocchi Gram-positivi antibiotico-resistenti specialmente in campo chirurgico ed intensivistico, raccomanda particolare attenzione all'atto della scelta di opzioni terapeutiche efficaci, portando al superamento sia delle eventuali resistenze microbiche, sia della barriera emato-encefalica, tale da determinare un'efficace penetrazione locale dei farmaci. Come nella maggior parte dei Paesi Occidentali, anche in Italia la frequenza di Staphylococcus aureus *meticillino-resistenti si dimostra particolarmente elevata, specialmente quando vi sono pazienti o situazioni ad elevato rischio. In occasione del trattamento delle infezioni del sistema nervoso centrale successive ad un intervento neurochirurgico (ascessi cerebrali e meningiti), un tema chiave è rappresentato dalle ridotte concentrazioni liquorali dei due antibiotici glicopeptidici disponibili (vancomicina e teicoplanina), in genere raccomandati come terapia di prima linea in corso di infezioni da cocchi Gram-positivi multiresistenti. Evidenze dalla letteratura internazionale hanno recentemente focalizzato il possibile ruolo di linezolid, un recente antibiotico oxazolidinonico, come candidato favorevole per il trattamento di gravi infezioni cerebrali (ascessi) e di processi infettivi post-neurochirurgici, laddove le opzioni terapeutiche e la loro efficacia siano significativamente limitate dal basso transfert emato-encefalico assicurato dai glicopeptidi, e dalla progressiva diffusione di ceppi batterici resistenti ai glicopeptidi. Tre casi clinici rappresentativi (due ascessi cerebrali ed una meningite batterica post-chirurgica), vengono presentati e discussi sulla base delle evidenze di letteratura disponibili: in tutti e tre i casi un trattamento di salvataggio con linezolid si è dimostrato risolutivo.*

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