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CLINICAL APPROACH AND MANAGEMENT OF BACTERIAL INFECTIONS OF THE CENTRAL NERVOUS SYSTEM RELATED TO HYDROCEPHALUS

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La Dra. Carmen Cabellos Mínguez, Profesora de la Facultad de Medicina de la Universidad de Barcelona y médico adjunta del Servicio de Enfermedades Infecciosas del Hospital Universitario de Bellvitge, hace constar que la tesis titulada

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Dra. Carmen Cabellos Mínguez

A mi familia

A mi otra familia: mis amigos

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1. *Listeria monocytogenes meningoencephalitis in adults: analysis of factors related to unfavourable outcome*. **Pelegrín I**, Moragas M, Suárez C, Ribera A, Verdaguer R, Martínez-Yelamos S, Rubio-Borrego F, Ariza J, Viladrich PF, Cabellos C. Infection 2014; 42: 817-27.

2. *Management of Ventriculoperitoneal Shunt Infections in Adults: Analysis of Risk Factors Associated with Treatment Failure*. **Pelegrín I**, Lora-Tamayo J, Gómez-Junyent J, Sabé N, García-Somoza D, Gabarrós A, Ariza J, Viladrich PF, Cabellos C. Clin Infect Dis 2017; 64: 989-997.

3. *In-vitro efficacy of a triclosan-impregnated external ventricular drainage catheter to prevent multi-drug-resistant Acinetobacter baumannii ventriculitis.* **Pelegrín I**, Ashraf W, Bayston R. Submitted for publication.

Book chapters

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Papers at scientific conferences

1. Efficacy of a triclosan impregnated external ventricular drainage catheter to prevent multi-drug-resistant Acinetobacter baumannii ventriculitis. **Pelegrin I**, Ashraf W, Bayston R. 25th European Congress in Clinical Microbiology and Infectious Diseases (ECCMID). Copenhagen, April 2015.

2. Hydrocephalus in adults with community acquired bacterial meningitis. **Pelegrín I**, Ariza J, Bayston R, Viladrich PF, Cabellos C. Hydrocephalus 2014, the Sixth Meeting of

the International Society for Hydrocephalus and CSF Disorders. Bristol, September 2014.

3. Neurological causes of death in adults with Listeria monocytogenes meningoencephalitis: Hydrocephalus and seizures. **Pelegrín I**, Viladrich PF, Ariza J, Cabellos C. 24th European Congress in Clinical Microbiology and Infectious Diseases (ECCMID). Barcelona, May 2014.

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INDEX

ABBREVIATIONS

C-ABM	Community-acquired bacterial meningitis
CNS	Central nervous system
CoNS	Coagulase-negative staphylococci
CSF	Cerebrospinal fluid
CT	Computed tomography
EVD	External ventricular drain
ELD	External lumbar drain
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
LMME	*Listeria Monocytogenes* Meningoencephalitis
VA	Ventriculoatrial
MDR	Multi-drug resistant
MIC	Minimal inhibitory concentration
OA	Only antibiotics
OSSR	One-stage shunt replacement
RE	Rhombencephalitis
SR	Shunt removal
TSB	Tryptone soya broth
TSSR	Two-stage shunt replacement
VP	Ventriculoperitoneal

INTRODUCTION

1. Hydrocephalus in the setting of community-acquired bacterial meningitis

1.1. General aspects of community-acquired bacterial meningitis

Community-acquired bacterial meningitis (C-ABM) is a serious acute illness associated with significant morbidity and mortality (1). The diagnostic methods are relatively simple, and effective antimicrobial agents and support therapies are available; nevertheless, C-ABM mortality is still approximately 15%, with notable variations between aetiologies, ranging from 5% for meningococcal meningitis to 20-30% for pneumococcal and *Listeria monocytogenes* meningitis. These latter aetiologies are usually the ones with the worst prognosis, and mortality is higher among neonates, the elderly and immunosuppressed patients (1-4).

Epidemiology and aetiology

The incidence of C-ABM varies throughout the world. In the UK and Western Europe, the incidence is 1–2 cases per 100,000 people per year, whereas it can reach 1000 cases per 100,000 inhabitants per year in the Sahel region of Africa (5-7). In a recent Dutch cohort, incidence of C-ABM declined from 1.72 cases per 100,000 adults per year in 2007-2008, to 0.94 cases per 100,000 inhabitants per year in 2013-2014 (7).

In “classic” surveillance studies that include all age groups, typically with a majority of cases occurring among children, *Haemophilus influenza*e, *Neisseria meningitidis*, and *Streptococcus pneumoniae* caused between 70% and 87% of the total (8, 9). However, the epidemiology of C-ABM has changed over the past 15 years due to the routine use of protein-polysaccharide conjugate vaccines in childhood against its common causative pathogens (10, 11). Since the introduction of these vaccines, the incidence of adult C-ABM has decreased substantially, partly due to the herd protection afforded by these paediatric conjugate vaccines according to US and Dutch studies (7). Meningitis due to *H. influenzae* type b has practically disappeared in several countries since the introduction of vaccination for children, while *S. pneumoniae* is also becoming less

frequent as an infant pathogen, although it remains an important cause of illness in the elderly due to the serotype replacement observed in adults (12).

In the Barcelona area, a prospective, observational study conducted in a university hospital to determine changes in the spectrum of adult patients with C-ABM over a 29-year period found that meningococcal meningitis decreased by 66% between 1996 and 2010, whereas meningitis by *L. monocytogenes* increased by 110% in comparison with the earlier period between 1982 and 1995. (13)

Thus, most cases of C-ABM in adults in Europe are caused by *S. pneumoniae* (53%). The incidence of meningococcal meningitis in adults has declined in the past decade, but it still represents around 27% of the episodes, mostly due to serogroup B (14).

Clinical characteristics and diagnosis

Multiple studies have been performed of the clinical characteristics of adults with C-ABM (4, 13, 15), and have highlighted that headache, fever, neck stiffness and altered mental status are common signs and symptoms at admission. The classic triad of fever, neck stiffness and altered mental status is reported in only 41-51% of patients (14), so the absence of these findings cannot be used to exclude the possibility of C-ABM.

The diagnosis of C-ABM requires CSF examination, including leukocyte count, glucose and protein levels, Gram staining and culture. CSF culture enables *in vitro* testing of the antimicrobial susceptibility patterns, after which antibiotic treatment can be optimized (16). If CSF Gram and culture are negative, CSF urinary pneumococcal antigen and CSF bacterial Polymerase Chain Reaction can provide additional information. Furthermore, blood cultures are a valuable tool for aiding detection of the causative organism.

Treatment

1. Antibiotic treatment

Antibiotics should be given as soon as possible to patients with suspected C-ABM, ideally after both blood and CSF have been obtained for culture. Early antibiotic treatment is associated with a lower mortality (17).

Empiric antibiotic treatment in C-ABM in adults includes ceftriaxone (4g/day) or cefotaxime (150mg/kg/day) plus ampicillin only if *L. monocytogenes* is suspected. The ESCMID guidelines (14) recommend its addition in adults over 50 years old and in those under this age who present risk factors for listeriosis like diabetes, pregnancy, use of immunosuppressive drugs and cancer.

The worldwide emergence of antimicrobial resistance, especially against *S pneumoniae*, affects the choice of empirical treatment in some countries. Penicillin-resistant pneumococci have been reported in all parts of the world (18) and have been associated with an increase in mortality (19). Vancomycin is widely recommended when penicillin-resistant pneumococci may be present, but because its penetration of the blood–brain barrier is poor some uncertainty remains regarding its benefit (20). Consequently, addition of vancomycin or rifampicin to cephalosporins in the empirical antibiotic treatment depends on the local risk of decreased susceptibility of *S. pneumoniae* (MIC> 2mg/L) (14), although successful cases of pneumococcal meningitis with MICs between 0.5-2 mg/L, treated empirically and definitively with high doses of cefotaxime (300mg/kg/day) have been reported (21). Specific antibiotic treatment should be optimized after identification of the causative microorganism.

2. Adjunctive dexamethasone treatment

Even in the presence of a susceptible organism, and despite apparently appropriate treatment, C-ABM accounts for a high number of deaths and neurologic sequelae. This is thought to be due to inflammatory processes. Therefore, efforts have focused on identifying useful adjunctive treatments that might reduce inflammation and brain oedema. The experimental research performed in the 1980s and 1990s into the pathophysiology of C-ABM concluded that adjuvant therapy such as dexamethasone must be effective for modulating the inflammatory response generated by the antibiotic treatment of meningitis (22). Nowadays, it seems clear that the use of dexamethasone reduces sequelae and mortality in pneumococcal meningitis and has a strong effect on hearing loss due to *H. influenzae* meningitis (23). Although its universal use or its use in different populations, aetiologies or situations is still

controversial, dexamethasone is considered standard in the treatment of pneumococcal meningitis, the aetiology with the highest mortality.

3. Other adjuvant treatments

Theoretically, osmotic agents such as glycerol can draw extravascular fluid from the brain into the vascular space and reduce intracranial pressure. The only osmotic diuretic to have undergone randomized evaluation is glycerol. A randomized controlled trial in children suggested that glycerol might be beneficial although their results have been controversial (25). However, the only randomized controlled trial in adults was stopped early because of an increased risk of death in patients in the glycerol group (26). As a conclusion, osmotic diuretics, including glycerol, should not be given to adults and children with bacterial meningitis according to a Cochrane Database Systematic Review published in 2013 (27).

Seizures occur frequently in C-ABM (15–24%) (1, 28, 29), especially in pneumococcal meningitis (28%) (30) and meningitis due to *L. monocytogenes* (7–17%) (31-33), and are associated with increased mortality (41%) (28). Antiepileptics as prophylaxis for in-hospital seizures have not been evaluated in randomized clinical trials. However, mannitol and phenytoin are used in clinical practice at some Spanish centres as treatment of pneumococcal meningitis (4, 34).

1.2. Hydrocephalus complicating community-acquired bacterial meningitis

Limited information is available about the timing of systemic and neurological complications in C-ABM. Fatality rates are still high and survivors often suffer long-term neurological sequelae such as impaired neuropsychological ability, or focal neurological deficits ranging from nerve palsy to hemiparesis (35-37). Frequently, these sequelae are the consequence of intracranial complications occurring during the course of the disease, such as intracranial haemorrhage, brain oedema, cerebritis, empyema sinus thrombosis, cerebral ischemia or hydrocephalus.

Hydrocephalus is a common medical condition characterized by abnormalities in the secretion, circulation and absorption of CSF, resulting in ventricle dilatation.

Physiopathology of hydrocephalus in C-ABM

The choroid plexus produces 400-500 ml CSF per 24h and the total CSF volume is 120-150 ml. Therefore, CSF recycles over three times per day, circulating in the CSF system and being absorbed in the subarachnoid space (38,39). This traditional theory has been challenged by a new working hypothesis, which suggests that CSF is permanently produced and absorbed in the whole CSF system as a consequence of filtration and reabsorption of water volume through the capillary walls into the surrounding brain issue (40, 41). In bacterial meningitis, the damage caused may influence the entire absorption system in the CSF circulation pathway, rather than a certain part. According to the clinical evidence, a large proportion of patients do not develop hydrocephalus because the absorptive capacity of CSF can compensate within a certain range; if the damage exceeds that range, hydrocephalus will occur. This may lead to different outcomes and this complex process can be summarized in the following three stages:

1. Compensatory stage of CSF absorption, with non-reversible clinical and image changes.
2. Decompensatory stage of CSF absorption, with possibly reversible clinical and image changes.
3. Hydrocephalus stage with severe non-reversible clinical and image changes; often diagnosed by the Evans Ratio or the bi-caudate index.

Particularly in meningitis, the loss of blood-brain barrier integrity leads to extracellular fluid accumulation and development of a vasogenic brain oedema. The phenomenon known as “resistance to CSF outflow” indicates decreased re-absorption of CSF and therefore accumulation. In the presence of these mechanisms, hydrocephalus complicating C-ABM has typically been classified as communicating; if the purulent exudate interferes with CSF absorption by the arachnoid villi or by obstructing the

foramina of Luschka and Magendie it is classified as obstructive, which is highly uncommon (42).

Clinical evidence of hydrocephalus complicating C-ABM

There is little clinical information about the epidemiology and outcomes of hydrocephalus complicating C-ABM exclusively in adult patients (43-46). Several important questions remain unanswered, including the proportion of hydrocephalus complicating C-ABM, the causative pathogens, and the long-term outcomes and the optimal management.

First of all, the exact frequency of hydrocephalus is not easy to study because of the different definitions of hydrocephalus. Different percentages and aetiologies of hydrocephalus complicating C-ABM have been reported. A Dutch national prospective cohort study reported a cumulative rate of hydrocephalus of 5% in adult C-ABM patients with an elevated risk associated with *L. monocytogenes* (43). However, a retrospective single centre study from Taiwan observed a cumulative rate of hydrocephalus complicating C-ABM of 21%, mostly caused by *Klebsiella pneumoniae* and viridans streptococci (44). Lastly, a study from northern Denmark published in 2013 reported a cumulative incidence of hydrocephalus in C-ABM of 3% during a 13-year period, mostly caused by *Escherichia coli* (45).

The most recent article published on this topic (46) concluded that enlarged brain ventricles in patients with C-ABM are associated with increased mortality, and that moresubtle changes in ventricle size other than evident hydrocephalus seem to be of clinical importance. All these changes impaired consciousness and reduced brain function in patients suffering from bacterial C-ABM and thus increased case fatality with an unfavourable outcome in 70% (43, 44, 47).

From the above, it seems that a clearer picture of the frequency and risk of this complication might help to improve therapy.

Little is known about the treatment of hydrocephalus complicating C-ABM. A potential treatment orientation based on the three-stage hypothesis would be to control the damage to the absorption system in the first and second stages in order to reduce

hydrocephalus occurrence, so that any drugs decreasing the inflammation response and preventing fibrosis could significantly reduce its development. In this connection, only one study has been published relating hydrocephalus and corticosteroids – an experimental meningitis study in rabbits, which found that the use of corticosteroids in the early stages of acute bacterial meningitis reduced CSF outflow resistance. In humans, it is not known whether dexamethasone, which is currently used in treatment of C-ABM, could contribute to this outcome.

Once hydrocephalus is established some patients require neurosurgical devices to control intracranial pressure either temporarily or permanently. These procedures have been associated with unfavourable outcomes (43). Not enough is known about the pathophysiology underlying the increasing ventricular size to be able to elucidate whether ventricular enlargement is an important step in the course of disease in C-ABM (46).

1.3. Particularities of community-acquired bacterial meningitis caused by *Listeria monocytogenes*

L. monocytogenes is a slow-growing food-borne intracellular pathogen that has become the third most common cause of C-ABM in adults (1). In recent decade a worldwide increase in the rate of LMME has been reported, with an estimated annual incidence in developed countries between 0.05 and 0.2 cases per 100,000 population (11, 48). Among the possible causes of this scenario is the higher prevalence of susceptible populations such as elderly patients and patients with impaired cellular immunity, which are both well-known predisposing factors for invasive listeriosis (49-51). This observation is of special concern, because mortality rates ranging from 17% to more than 30% have repeatedly been reported in LMME (1, 32, 33, 52, 53). The high mortality rates accompanying this disease may be favoured above all by the frequently poor underlying condition of the host; the specific role of other factors influencing the prognosis of these patients is not well defined. Indeed, few data are currently available regarding the relevance of hydrocephalus, a commonly reported complication (15%), and of other neurological findings (43).

L. monocytogenes has some differential features that distinguish it from the other two more frequent causes of C-ABM. In most cases it presents with a subacute development of disease; in a large proportion of patients, symptoms were present for ≥4 days (27%) (33). Moreover, while meningitis is the commonest form of LMME, the frequency of rhombencephalitis among all patients with CNS listerial infection varies considerably between series (54), probably indicating that this condition is underdiagnosed. Approximately 10% of CNS listerial infection manifest as macroscopic brain abscesses (50).

Standard therapy has been amoxicillin, ampicillin or penicillin G +/- aminoglycosides (55). The latest research into LMME has focused on the analysis of an optimal choice of antibiotic therapy, and some authors have suggested that the addition of aminoglycosides may be deleterious due to an association with renal impairment (42,52,56). Consequently, ESCMID guidelines promote caution in using additional gentamicin in the treatment of LMME (14). However, a very recent nationwide prospective observational study in France including 427 cases of bacteraemia and 252 cases of neurolisteriosis argued that the use of beta-lactams and aminoglycosides or cotrimoxazole could improve survival more than other antibiotics, independently of any associated factor (57). Duration of LMME treatment is based on empiric data and traditionally 21 days or longer has been enough to achieve cure. Shorter treatments (two weeks or less) have not shown efficacy (58). The guideline committee of ESCMID concluded that dexamethasone should be stopped if *L. monocytogenes* is isolated (14). This is based on a Dutch study that was performed to clarify the role of dexamethasone in LMME and showed a high rate of unfavourable outcome (61%) and mortality (36%) (59). Moreover, a recent French study (57) showed for the first time a significant reduction in survival in patients with neurolisteriosis treated with adjunctive dexamethasone. These results suggest that dexamethasone should be avoided in the treatment of neurolisteriosis.

2. Infections associated with CSF devices used for hydrocephalus

Hydrocephalus is a common neurosurgical disease, affecting approximately 40 per 100,000 people and requiring CSF diversion devices for its management (60). In case of chronic hydrocephalus, a permanent device may be necessary and this can be achieved by an internalized CSF shunt system. In case of an acute rise of intracranial pressure which compromises CSF circulation, for example, after intracerebral bleeding, tumour surgery or meningitis, temporary percutaneous CSF drainage can be achieved by an EVD or ELD.

Infection is one of the most serious complications after CSF shunt or EVD placement, increasing both mortality and morbidity (61). It also raises both economic and personal costs (62) since it increases the reoperation rate and prolongs hospital stay (63).

2.1 General aspects of CSF shunt infections

CSF shunts have three main components –a proximal ventricular catheter, a unidirectional valve, and a distal catheter –, which drain excess CSF from the cerebral ventricles, usually into the peritoneal cavity (VP) or less commonly into the right cardiac atrium (VA). The third type of CSF shunt more used is the lumboperitoneal, which diverts CSF from the spinal space in the lower back to the abdomen and it can be used to treat non-obstructive hydrocephalus.

Overall, today VP shunts are the most frequently used permanent CSF diversion device and have dramatically reduced the morbidity and mortality rates associated with hydrocephalus since their introduction in the 1970s (64). Although the incidence of shunt infections has generally fallen, it is still unacceptably high, with a rate ranging from 5.6% to 12.9% (65).

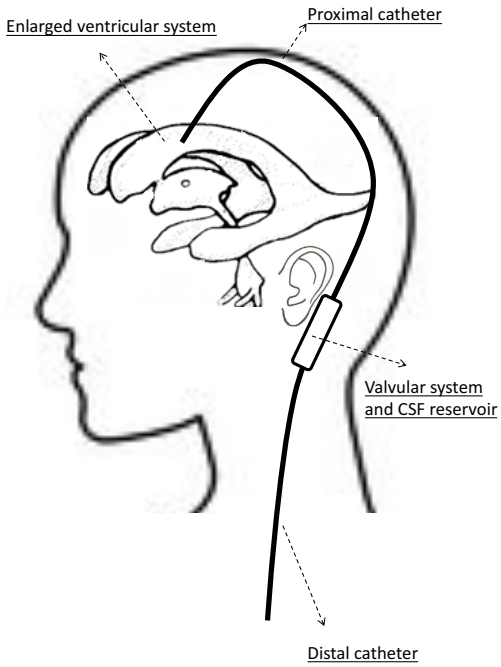


Figure 1. Components of a CSF shunt. The distal catheter usually goes to the peritoneal cavity (VP) or to the right cardiac atrium (VA).

Aetiology, pathogenesis and biofilm formation

The majority of CSF shunt infections are caused by coagulase-negative staphylococci, with fewer caused by *Staphylococcus aureus* (5-18%) and *Propionibacterium acnes* (9%). Polymicrobial shunt infection rates range between 12-15% and Gram-negative bacilli 4-7% (66, 67). The source of the organisms is almost invariably the patient's skin, from which they gain access to the device during its insertion (68, 69). Even after thorough skin preparation, resident bacteria may remain in follicles and it is therefore not unusual to find staphylococci in the incision during the procedure. There are also other routes of infection such as skin dehiscence over the shunt tract, hematogenous spread and bowel perforation by the distal catheter tip, resulting in an ascending infection (66).

Microorganisms, particularly staphylococci, are highly likely to adhere to, and colonize, the inner surfaces of the shunt. After adhering, they multiply and produce copious amounts of exopolysaccharide ('slime'). Biofilms are currently defined by morphologic criteria as "an aggregate of microbial cells adherent to a living or non-living surface,

embedded within a matrix of extracellular polysaccharides" (70); their growth is very slow, which accounts for the often long periods between surgery and the clinical presentation of infection.

Clinical and diagnostic dilemmas

VP infection may be insidious and nonspecific, with variable clinical features that depend on the site of the infection and the responsible microorganism. The time from VP shunt placement to clinical debut often ranges between 6 and 9 months after surgery (71, 72). Fever is present in fewer than 50% of cases and is usually intermittent and mild, while there may be abdominal discomfort or tenderness and/or erythema over the lower shunt track. However, the most frequent symptom is obstruction at the distal end, and the differential diagnosis that the neurosurgeon and the infectious disease specialist should consider is between infective and non-infective shunt obstruction (in which these features are absent).

Aspiration of CSF from the shunt must be centrifuged for Gram film and culture, whatever the cell count, because bacteria are quite frequently found in the absence of a significant cellular response. Isolates should be kept and identified, particularly if they are also seen on Gram film, in which case they usually indicate shunt infection. CSF cultures obtained from shunts have been recommended to be incubated for at least 10 days because growth of P. acnes may take longer than a conventional culture (73). The presence of a negative CSF culture should not definitively rule out diagnosis if symptoms and a suggestive history are present.

2.2. Management of ventriculoperitoneal shunt infections

Once the diagnosis of a VP shunt infection is made, the mainstay of treatment includes antibiotics with or without surgical management. Three factors influence the choice of antimicrobial therapy of VP shunt infections:

1. The mode of growth of the organisms in the shunt lumen. The concentration of antimicrobials required to kill biofilm organisms is often several logs higher than the conventional minimum inhibitory concentration (74).
2. The inherent multi-resistance of many strains of coagulase-negative staphylococci. Almost all are resistant to penicillin; at least 50% are resistant to oxacillin and therefore to cephalosporins, which are commonly used to treat bacterial infections of the CNS.
3. Lack of a vigorous inflammatory response in the CNS, meaning that most systemically administered antimicrobials fail to penetrate into the CSF; this is particularly true of aminoglycosides, beta-lactams and glycopeptides. Of the few drugs that give acceptable CSF concentrations in these circumstances, rifampicin is highly active against most organisms causing shunt infections but cannot be given alone because of the rapid development of resistance.

These factors explain the generally disappointing results achieved whenever attempts are made to treat VP shunt infections without shunt removal. Antibiotic therapy alone, administered systemically or intraventricularly, or by both methods offers limited efficacy in the management of VP shunt infection (75, 76) and expert recommendations state that a combination of antibiotic and surgical treatment is required to achieve the best chance of definitive cure. These recommendations are based on case series, expert opinion, and a single prospective randomized study published decades ago (75).

A review of the literature reveals two classical surgical approaches to the management of an infected shunt.

1. A two-stage shunt replacement consisting of early shunt removal and an EVD inserted to control CSF pressure, if necessary, followed by the replacement of the shunt when the CSF is sterile.
2. A one-stage shunt replacement after externalization of the distal shunt catheter, followed by CSF sterilization with intravenous/intrashunt antibiotic treatment.

Despite the major consequences of infection, and although physicians have more than 50 years of experience with this problem, no attempts have been made to identify risk factors for treatment failure in episodes of VP shunt infection in adults (77, 78). The latest research has focused on the prevention of VP shunt infection by implementing standardized protocols (79) or by using antimicrobial impregnated/silver processed CSF shunts (80).

Hydrocephalus, estimated to affect nearly 1 in every 500 children, (81), is one of the most common paediatric pathologies requiring neurosurgical intervention. For this reason, previous studies have evaluated CSF shunt infections predominantly in this population, and data regarding CSF shunt infection in adults are very limited. In addition, these studies always include patients with different types of CSF shunts such as VA, VP and lumboperitoenal; none of them included patients carrying only a VP shunt (66, 67, 76, 82), which has meant that the results vary widely.

The initial therapeutic approach is of paramount importance because treatment failure may make additional surgery and supplementary antibiotic courses necessary, lengthening hospital stay and increasing the risk of nosocomial infections. Moreover, the optimal route of administration and duration of antibiotics are yet to be established, as are the risk of potential superinfection of CSF temporary drainages or externalized peritoneal VP shunt catheters, and the best timing for shunt exchange. However, the Infectious Diseases Society of America published clinical practice guidelines for healthcare-associated ventriculitis and meningitis (83) to provide recommendations for these issues. The optimal management of device-associated infections is currently being investigated.

2.3 General aspects of external ventricular drain associated infection

EVDs are used for the diagnosis and treatment of raised intracranial pressure, after head trauma, intracranial haemorrhage or tumours obstructing the CSF circulation, and they may be in place for a few days or up to 2–3 weeks. As the system is not

totally internalized, and as CSF is often extracted from it for analysis and pressure monitoring, the risk of infection is high, with rates of up to 20% (84, 85). These infections may be difficult to diagnose because changes in CSF parameters are often subtle, making it hard to determine whether the abnormalities are related to infection, related to placement of devices, or are due to the neurosurgery.

The most commonly found pathogens in EVD-associated infections have traditionally been skin flora, mostly staphylococci (85). Today, however, the epidemiology of EVD-associated infections has changed and Gram-negative bacteria have emerged as a considerable problem, especially in intensive care units where multi-resistant strains causing infection are increasing. In particular, *Acinetobacter baumannii* has been increasingly reported to cause nosocomial ventriculitis (86, 87) with a mortality rate up to 73% (88.) Due to its ability to cause outbreaks and to become resistant to antibiotics, the World Health Organization has registered it as a nosocomial pathogen in which resistance is a matter of great public health concern (89).

Early and appropriate antimicrobial therapy has been associated with better clinical outcomes. The agents chosen must be active against the organisms most likely to be encountered based on local epidemiologic trends, and must achieve adequate concentration in the CNS. In this regard, treatment options for multi-resistant infections, such as MDR *A. baumannii* CNS infections, may be limited (90). In these cases, the use of intrathecal antimicrobials might be the only therapeutic choice but at present there are no reliable clinical data supporting their use.

2.4 Prevention of external ventricular drain associated infection

Ventriculitis may generally result from contamination of the drain during insertion and manipulation and by its colonization at the insertion site by skin flora. Prevention can be targeted to these potential routes of infection (60). Risk factors related to infection include the indication for catheter placement, duration of catheterization, differences in placement technique, antimicrobial use, frequency of manipulation and sampling, and CSF leaking.

Understanding the risk factors for infection can help guide prevention efforts. The new emphasis on health care–associated infections has led to the study of novel methods to decrease catheter-associated infections, with encouraging results (91, 92). One of these approaches, known as care bundles, groups together best practices for a disease process, which improve care when used individually, but result in a substantially greater improvement when applied together. In recent years, the use of bundles has also been trialled to prevent EVD-associated infections, with a protocol violation as a significant risk factor for failure (93, 94).

The use of prophylactic antimicrobials in neurosurgical patients with EVDs is controversial, with no standard protocols or well-studied recommendations. Furthermore, antibiotic-impregnated EVD catheters have recently been introduced in an attempt to reduce the risk of ventriculitis, with reports of a significant decrease in infection rates (95-98). At present only two types of antimicrobial-impregnated catheters are available – minocycline/rifampicin or clindamycin/rifampicin – both of which specifically target staphylococcal infections. No difference in efficacy has been found, and institutional preference usually dictates use.

These antibiotic-impregnated EVD catheters containing rifampicin and clindamycin target Gram-positive bacteria, mainly coagulase-negative staphylococci, which are the most common cause (60). In this setting, new antimicrobial-impregnated EVD with potential activity against Gram-positive and Gram-negative bacteria are needed, especially those caused by multi-resistant Gram-negative bacilli.

HYPHOTESIS

AND RATIONALE OF THE DOCTORAL PROJECT

Among infectious diseases, those involving the CNS pose a unique challenge to physicians, due both to the potential morbidity and mortality that they cause and to the inherent difficulties involved in their treatment. Despite further progress in antimicrobial and adjuvant therapy of C-ABM in recent decades, mortality and long-term disabling sequelae remain substantial. Accurate information regarding new emerging aetiologies and the related complications are crucial today to ensure appropriate management and to improve outcome. Furthermore, prevention and treatment of CSF device infections remains a challenge for infectious disease specialists due to the presence of bacterial biofilm. Very few prospective studies, including clinical trials, of the management of CSF shunt infections have been carried out and the retrospective observational studies performed to date have included small, undetailed and heterogeneous samples. In this setting, observational studies are very valuable and they might be the only feasible studies to carry out. The most frequent problem for undertaking clinical trial is the recruitment of a requisite number of study subjects, and moreover, the heterogeneous management between hospitals make difficult to follow a protocol.

This thesis aims to address some of these aspects from the perspective of an infectious disease specialist. The prognosis of C-ABM has improved in recent years and knowledge of the entire clinical spectrum of complications and their prompt detection are a prerequisite for improved management of the disease. One complication that has not been explored in depth is hydrocephalus, which may worsen the prognosis. Furthermore, the epidemiology of C-ABM has changed recently; *L. monocytogenes* has become the third most important cause of C-ABM worldwide and may be associated with higher rates of hydrocephalus. Once hydrocephalus is established, temporary or permanent CSF devices may be needed to solve it, but may themselves increase the risk of infection. Regarding the management of CSF shunt infections, removal of the infected CSF shunt might be crucial for achieving cure due to the production of biofilm associated with these infections, but how and when it should be removed are issues that have not been conclusively established. Regarding EVD-associated infections, in the past two decades major progress has been made by the introduction of bundles and antimicrobial-impregnated catheters, but the shifting epidemiology to Gram-negative bacteria has rendered these measures insufficient. A new impregnated

antimicrobial catheter with a new combination of antibiotics targeting Gram-positive and Gram-negative bacteria might decrease this risk of ventriculitis.

Providing answers to these clinically unresolved problems requires the participation of an experienced clinical team with expertise in the management of bacterial infections of the CNS. The Department of Infectious Diseases and the Department of Neurosurgery at the Hospital Universitari de Bellvitge have many years of experience in the management of C-ABM and neurosurgical infections. In particular, the infectious disease specialist Prof. Pedro Fernández Viladrich founded this line of research and with Dr. Carmen Cabellos, the supervisor of this thesis, has evaluated several aspects of C-ABM and neurosurgical infections. This group has become a reference point in Spain for bacterial infections of the CNS due to their everyday clinical work with neurosurgeons over more than 40 years, combined with academic studies as part of clinical and experimental research projects, clinical guidelines, and many publications in high-ranking journals.

The doctoral candidate has had the chance to be a part of this medical team and evaluates patients with community and nosocomial-acquired infections on a daily basis, creating and updating the clinical databases used in the clinical studies.

Furthermore, the group has extensive experience with experimental bacterial meningitis models in rabbits, which have traditionally provided answers to unsolved clinical problems. In this regard, the collaboration with Professor Bayston from the Biomaterials infection-related group at Nottingham University (Nottingham, UK) has given the candidate the chance to carry out *in vitro* testing of a new antimicrobial catheter against MDR *A. baumanni.*

All the studies presented in this thesis provide new information on different clinical aspects and management regarding bacterial infections of the CNS related to hydrocephalus.

AIMS

A. Hydrocephalus complicating Community-Acquired Bacterial Meningitis

A.1. Hydrocephalus in adults with C-ABM.

Aim 1. To evaluate the occurrence, clinical characteristics and treatment of patients with hydrocephalus complicating C-ABM.

Aim 2. To measure the impact of complicating hydrocephalus in the outcome of patients with C-ABM.

Aim 3. To determine risk factors for development of hydrocephalus in C-ABM.

A.2 *L. monocytogenes* meningoencephalitis.

Aim 1. To evaluate the efficacy of antibiotic and adjuvant therapy in LMME patients.

Aim 2. To analyse the risk factors for mortality and sequelae in LMME patients.

B. Prevention and treatment of infection of CSF devices used for hydrocephalus

B.1. Management of VP shunt infections in adults.

Aim 1. To assess the efficacy of the treatment strategies in an adult cohort of VP shunt infections.

Aim 2. To identify risk factors predicting treatment failure in the treatment of VP shunt infection.

B2. Prevention of EVD-associated infections

Aim 1. To assess the *in vitro* antibacterial activity of a new impregnated external ventricular drainage catheter against MDR *A. baumannii.*

METHODS

1. Clinical research

1.1. Setting

The Hospital Universitari de Bellvitge is an 800-bed teaching hospital in the urban area of Barcelona, Spain, with a referral population of one million. Patients with bacterial infections of the CNS are attended by a multidisciplinary team of infectious disease specialists, neurosurgeons, neuro-radiologists, intensive care specialists, neurologists, hospital pharmacists and microbiologists.

Patients are admitted to the infectious diseases unit, neurology unit, critical care unit or the neurosurgery unit, which includes a semi-critical care area.

Patients commonly admitted to these units include C-ABM, encephalitis, subdural and epidural empyema, brain abscess, CSF device-related infections, and surgical site infections after craniotomy or spine surgery.

1.2. Clinical approach to bacterial infections of the CNS

1.2.1. Community-Acquired Bacterial Meningitis

Clinical and microbiological studies

An initial lumbar puncture and blood cultures were performed in all cases of suspected C-ABM. CSF samples were submitted for Gram stain, bacterial cultures, and cytochemical tests. After centrifugation of CSF specimens, the resulting sediment was used to prepare smears for microscopic examination and to inoculate blood and chocolate agar plates and thioglycolate broth. Microbiological identification was performed according to standard methods (99). Antibiotic susceptibilities were determined by disk-diffusion, complemented, if necessary, by determination of MICs and minimum bactericidal concentrations (100). CT scan was not routinely performed. Generally, in the emergency room a CT scan before lumbar puncture was not indicated

if the suspicion was C-ABM; it was only mandatory if the clinical course lasted for more than 48 hours or in the event of focal neurologic deficit or coma. Similarly, during admission it was only performed, if complications were suspected.

Definitions

C-ABM was diagnosed in patients with compatible clinical findings suggestive of meningitis and inflammatory CSF, with polymorphonuclear pleocytosis (white blood cells 100/mm and predominant neutrophils). Aetiology was assigned by one or more positive results for the following: Gram stain, CSF culture, blood culture, CSF urinary pneumococcal antigen and/or CSF bacterial Polymerase Chain Reaction.

When CSF Gram stain and CSF and blood cultures were negative, the C-ABM was considered to be of unknown origin, although it was accepted as meningococcal aetiology when characteristic skin lesions were present.

LMME was diagnosed in patients with compatible clinical findings suggestive of meningitis or rhombencephalitis and positive CSF culture for *L. monocytogenes* and/or positive blood culture for *L. monocytogenes* and CSF pleocytosis (5 cells/mm3). The diagnosis of rhombencephalitis required clinical evidence of brainstem and/or cerebellum involvement (ataxia or cranial nerve involvement, plus spinothalamic tract, corticospinal tract, or posterior column abnormalities) or a conclusive neuroimaging study. Time to presentation was defined as the time from onset of symptoms to the first dose of an appropriate antibiotic therapy. Time to presentation was defined as late if longer than two days and very late if longer than four days. Patients were defined as having ‘‘Underlying conditions’’ if at least one of the following were present in the medical record: diabetes mellitus, hepatic cirrhosis, solid and hematologic neoplasm, chronic corticosteroid therapy and other immunosuppression comorbidities. Corticosteroid therapy was defined as 5 mg/24 h of prednisone or an equivalent dose of another corticosteroid. Immunosuppression was considered if other illnesses or treatments that cause immunosuppression were present. Hydrocephalus was diagnosed on the basis of clinical symptoms and measurement of Evans’s index in CT (101, 102). Presence of seizures was defined by the criteria of the ‘‘International Classification of Seizures’’ and ‘‘International Classification of Epilepsies

and Epilepsy syndromes''. Impairment of renal function was defined as a doubling of the serum creatinine level or a level of 150 umol/L.

Management and outcome

Antibiotic use has changed over the years according to resistance patterns. Penicillin or chloramphenicol was used until 1984, replaced later by cefotaxime or ceftriaxone with or without ampicillin (103). Intravenous administration of penicillin, ampicillin, vancomycin, a carbapenem or cotrimoxazole was considered adequate empirical treatment in case of LMME.

Since 1987, all patients at our institution with suspected pneumococcal meningitis and/or patients with meningitis with intracranial hypertension (30 cmH_2O) in the emergency room have been routinely treated with dexamethasone 4 mg/6 h for 48 h, eight doses in total, beginning 10–15 min before antibiotic therapy with a double first dose. Anti-seizure prophylaxis with phenytoin at a loading dose of 18 mg/kg, is followed 24 h later by a maintenance dose (2 mg/Kg/8 h) during 10 days, immediately after antibiotic therapy. Since 2003, after the publication of results of a European controlled trial in C-ABM (22), adjuvant treatment with dexamethasone has been administered in most cases with suspicion of bacterial meningitis at our centre with the previously mentioned schedule. For this reason, some patients with LMME also received this treatment.

After discharge they were assessed at the outpatient clinic within the following four weeks and three months after the episode. Neurologic sequelae were evaluated at the outpatient clinic and diagnosed if they were present three months after discharge. Mortality was defined during hospitalization and classified as early if it occurred in the first week after admission and late if it occurred more than one week after admission.

1.2.2. CSF shunt infections

Clinical and microbiological studies

CSF samples were obtained from an aseptic puncture of the CSF reservoir, through the externalized peritoneal catheter, or via lumbar puncture. Microorganisms were identified according to standard criteria (104) after samples had been seeded in thioglycolate broth and 5% sheep blood and chocolate agar and incubated for 10 days.

Definitions

An episode of infection was defined as the presence of clinical features compatible with a positive culture from CSF, VP shunt tip, or from exudate swabs obtained from wounds overlying the implant material. The time to infection was established as the number of days between the placement of the VP shunt or its last surgical revision and the onset of symptoms. Coma was defined when patients scored ≤8 in the Glasgow Coma Scale at admission (105). Hydrocephalus at admission was diagnosed following Evans's criteria and considered when ventricular size was larger than in a previous computed tomography scan. CSF sterilization time was established as the number of days between the initiation of therapy and first negative CSF culture.

Antibiotic and surgical management

In all patients with a suspected VP shunt infection, blood cultures and a CSF sample were recovered. Distal externalization of the peritoneal catheter was performed in cases of a strong suspicion of infection and/or malfunction. After these procedures, all patients followed our empirical treatment protocol, which has been in place since 1985: intravenous vancomycin 1 g twice daily ± ceftazidime or meropenem 2g 3 times daily. Before 1985, several empirical combinations of antibiotics included cloxacillin or vancomycin ± aminoglycosides or antipseudomonal penicillins. Once antimicrobial susceptibility was available, antibiotics were adjusted accordingly. The treatment strategies for all VP shunt infection episodes were classified under the following four

headings based on an intention-to-treat analysis: OA without VP shunt removal; SR without shunt replacement; OSSR, that is, the VP is removed and replaced by a new device in a 1-step exchange procedure, ideally after the CSF has been sterilized with antibiotics; and TSSR, that is, a first surgical step to remove the VP shunt, a shunt-free time under antibiotic treatment in order to sterilize the CSF, and a second surgical procedure to re-implant a new device. The need for EVD/ELD depended on the type of underlying neurological disorder. The four types of strategies included intravenous ± intraventricular antibiotics. The decision to initiate surgical and antimicrobial therapy was made by the neurosurgeon and the infectious diseases consultant. When the first chosen strategy failed, a salvage therapy was provided, if feasible.

Outcome and follow-up

Follow-up was recorded by review of hospital admissions and outpatient clinic visits. The primary endpoint was failure of the first treatment strategy and was defined as the lack of definite CSF sterilization within 14 days or related mortality. Cure was defined as cessation of initial symptoms and signs of infection and a negative CSF culture after treatment, if available. Mortality was recorded during hospital stay and was classified as related to the VP shunt infection if death occurred during treatment and was due directly to a persistent infection or its complications.

1.3 Study design and statistical analysis

The clinical studies included in this thesis comprise three observational studies, retrospective analyses of prospectively gathered data. The data on C-ABM and CSF shunt infections are collected following a defined protocol (Annexes I and II). This information is critically reviewed and introduced in a Microsoft Access database.

Since January 1977, all cases of C-ABM have been prospectively recorded in a database, which we used to retrospectively select patients who developed hydrocephalus complicating C-ABM between January 1977 and January 2011. Then we

retrospectively identified all cases of LMME among C-ABM between January 1977 and December 2009, and also included cases presenting as rhombencephalitis.

All episodes of VP shunt infection in patients aged ≥12 years between 1980 and 2014 were prospectively identified and recorded.

Statistical analysis was made with the SPSS (Statistical Package for the Social Sciences) software (version 18.0 or higher). In general, categorical data were compared using the Chi-square test or Fisher's exact test, and continuous data with the t test or Mann–Whitney U test, as appropriate. Furthermore, outcomes were evaluated using univariate analysis and multivariate logistic regression analysis.

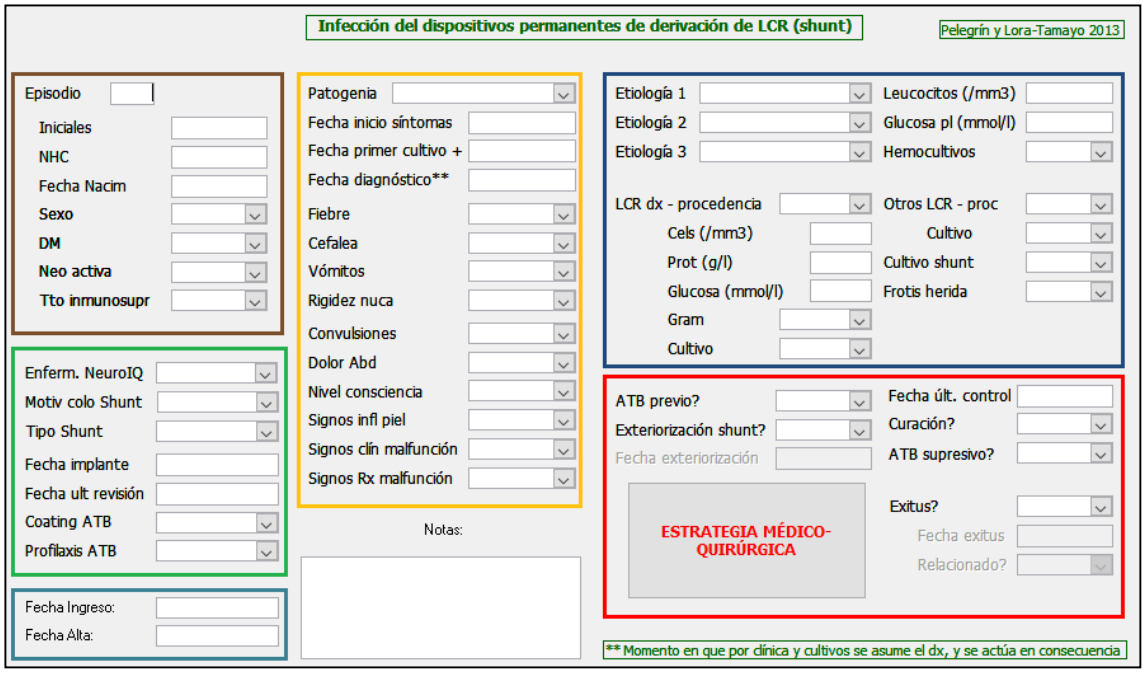


Figure 2. Access database in our center for the cohort of CSF shunt infection.

2. Experimental Research

2.1 Setting

The University of Nottingham is one of the leading universities in the UK and Europe. The university's Biomaterials Infection Related Group investigates the causes and mechanisms of surgical infection, particularly those involving implantable devices, so as to advance the treatment and prevention of these infections. The head of the group, Prof. Bayston, has developed a novel (patented) method of conferring long-term antimicrobial activity on polymeric implants, which led to the development and commercialization of an antimicrobial hydrocephalus shunt which is now used by approximately 930,000 patients all over the world and has had a significant impact on infection rates. As the technology has developed, it has been applied for dialysis and permanent urinary catheters (106-108).

To study the activity of a new impregnated antimicrobial catheter, the doctoral candidate moved to Nottingham (UK), and under the supervision of Prof. Bayston tested the catheter *in vitro* with a dynamic model in the laboratories of the Department of Orthopaedics, Trauma and Sport Medicine at the Queen's Medical Centre.

Fig 3. Laboratory at Department of Orthopaedics, Trauma and Sport Medicine, located at the Queen's Medical Centre.

2.2 Laboratory tests

2.2.1. Biomaterials

Medical grade silicone tubing, barium filled, internal diameter 1.5mm, external diameter 3 mm [Dow Corning Europe, Seneffe, Belgium] was used as controls.

2.2.2 Impregnation process

Thirty-five cm lengths of silicone tubing were impregnated using a previously published method (109). Briefly, the antimicrobials chosen (rifampicin R3501, trimethoprim base T7883, and triclosan (Irgasan), all from Sigma-Aldrich, Poole, UK, were dissolved in chloroform to give concentrations (w/v) of 0.2% rifampicin, 1% trimethoprim and 1% triclosan. The silicone tubing was immersed in the solution at room temperature for 1 h, during which it swelled to approximately twice the original volume. The tubes were then removed, briefly rinsed in ethanol and air-dried overnight, during which time they returned to their original dimensions. During this period, the molecules of antimicrobial dispersed evenly throughout the silicone matrix. Antimicrobial and plain tubing controls were packaged and sterilized by autoclaving at 121°C for 15 min.

Fig 4. Silicone-impregnated tubing with 0.2% rifampin, 1% trimethoprim and 1% triclosan. The original white tubing turned orange due to rifampin.

2.2.3 Test bacteria

A. baumannii isolates used in this study were from cases of EVD ventriculitis at Queen's Medical Centre in Nottingham, UK (F1865); a gift from Dr Mark Enwright, University College Hospital, London, UK (F2653); and a gift from Sheba Medical Centre, Ramat Gan, Israel (F3859). They were characterized using conventional methods: Gram stain, oxidase test, biochemical profiling (API 20NE, BioMérieux, Basingstoke, UK) and growth at 44°C. Matrix Assisted Laser Desorption Ionization Time-of-Flight (MALDI-TOF) technology was used to confirm the phenotypic identification. Antibiotic susceptibility was determined using disk diffusion and interpreted following the CLSI criteria. Twelve antibiotics (Oxoid Ltd, Basingstoke, UK) were tested. Multidrug resistance was considered when resistance was found in more than two of the following five drug classes: antipseudomonal cephalosporins (ceftazidime or cefepime), antipseudomonal carbapenems (imipenem or meropenem), amoxicillin/ clavulanate, fluoroquinolones (ciprofloxacin), and aminoglycosides (gentamicin) (110). MICs of rifampicin and trimethoprim were determined using E-test strips (AB Biodisk, Solna, Sweden). MICs and minimum bactericidal concentrations of triclosan were determined using broth microdilutions in triplicate.

2.2.4. Biofilm formation assay

The ability of *A. baumannii* strains to form biofilm was measured using a microtitre plate assay. Overnight suspensions of F1865, F2653 and F3859 prepared in 100% Tryptone Soya Broth (TSB, Oxoid) to early log phase in a 37°C shaker incubator at 190 revolutions per minute for 4h were adjusted to A_{490} 0.6. The bacterial suspension was dispensed in 200 µL volumes in 96-well polystyrene microtitre plates and incubated for 24 h at 37°C. After removal of the medium, plates were washed twice with phosphate-buffered saline solution, fixed with 150 µL of methanol and airdried. Biofilm was stained with 150 µL of 2% crystal violet solution for 15 min. After a gentle wash with distilled water, the plates were again airdried before the biofilm-associated dye was solubilized with 150 µL of 100% ethanol. 100 µL of this solution was transferred to a new 96-well microtitre well and the A_{490} of each well was measured using an

automated microtitre-plate reader (BioTek ELx800^{TM}). All tests were carried out three times.

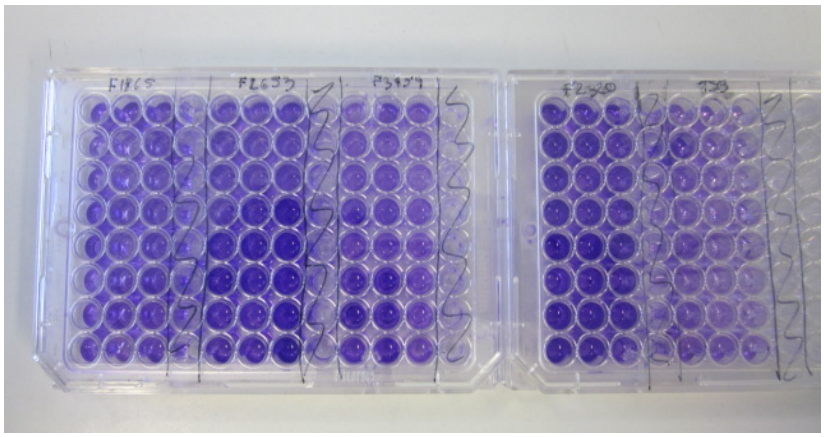


Fig 5. Crystal violet assay with F1865, F2653, F3859 showing A. baumannii biofilm compared to a positive and negative control.

2.2.5 Measurement of bacterial adhesion to plain silicone

Tests of attachment were carried out to detect any difference between the three strains (F1865, F2653 and F3859), which were grown in 100% TSB to early log phase in a 37°C shaker incubator at 190 revolutions per mintue for 4 h. They were then centrifuged for 20 min and re-suspended in a TSB concentration, typically 0.125%, previously determined by experiment for each strain to allow the bacteria to survive in the medium but not to replicate. Autoclaved plain 1 cm silicone tube segments were immersed in 1:1000 diluted human plasma (NHSBT, Watford, UK) for 1 h at 37°C to develop a conditioning film. After rinsing, they were exposed to the bacterial suspensions, adjusted to A490 0.8-0.9 (10^8 cfu/mL) and then diluted to 10^6 cfu/mL, for 1 h at 37°C. They were then removed and sonicated for 5 min at 50 Hz. Viable bacteria in the sonicate were enumerated by spreading onto Sheep Blood Agar (Oxoid) and incubating at 37°C for up to 48 h.

2.2.6. Determination of time to kill bacteria (tK100)

The tK100 is designed to determine the time taken to kill 100% of a challenge of bacteria attached to the biomaterial (111). The bacterial test strains (F1865, F2653 and F3859) were grown in 100% TSB to early log phase in a 37°C shaker incubator at 190 revolutions per minute for 4 h. They were then centrifuged for 20 min and re-

suspended in a previously determined TSB concentration (0.125%) that would allow each strain to survive in the medium but not to replicate. Human plasma conditioning film was applied as described above. After rinsing, the plasma-coated impregnated segments were exposed for 1 h at 37°C to the bacterial suspensions, adjusted to A490 0.8-0.9 (10^8 cfu/mL) and then diluted to 10^6 cfu/mL. They were then rinsed and immersed in dilute TSB concentration and incubated at 37°C. Every day the segments were removed and immersed in fresh dilute TSB. At intervals of 0, 24, 48 and 72 h, three segments of each series were removed and sonicated for 5 min at 50 Hz. Viable bacteria in the sonicate were enumerated by spreading onto Sheep Blood Agar and incubating at 37°C for up to 48 h. Plain silicone control 1 cm segments were treated in exactly the same way as impregnated segments.

2.2.7 In vitro challenge

The *in vitro* challenge is designed to determine the ability of impregnated catheter tubing to resist bacterial colonization with multiple bacterial challenges in flow conditions (109). The apparatus is modular and consists of a series of glass cylinders. The autoclaved test catheter tubes (35 cm in length) were aseptically introduced through the glass cylinders which were then filled with distilled water. The lumens of the catheters were perfused with 2% TSB from a reservoir by means of a pump at 20 mL/h and this was discharged into a waste collection vessel. The system was maintained in an incubator set at 37°C. F1865, F2653 and F3859 were used to challenge the test and plain tubing controls in triplicate. The test bacteria were grown in 20 mL TSB for 4 h on a 37°C shaker incubator set at 190 rpm and the A490 adjusted to 0.8-0.9 (10^8 cfu/mL) and then diluted to 10^4 cfu/mL. To challenge the catheters, perfusion was stopped and 1 mL of bacterial suspension was aseptically inoculated down the catheters. Clamps were applied for 1 h to allow attachment. Clamps were then removed and perfusion was re-started. Samples of effluent were aseptically collected periodically from the outlet of the catheters for determination of viable count. The catheters were re-challenged with new controls every two weeks if the bacteria had been cleared and there was no evidence of colonization by that time, and this regimen was continued for 42 days. At day 42, the successfully impregnated

catheters were removed from the apparatus and were aseptically filled with 200 µL of sterile water and clamped at both ends. They were then sonicated for 5 min at 50 Hz and 100 µL of the lumen sonicate was spread onto Sheep Blood Agar (Oxoid) and incubated at 37°C for up to 48 h. Gram staining of the sonicates was also performed.

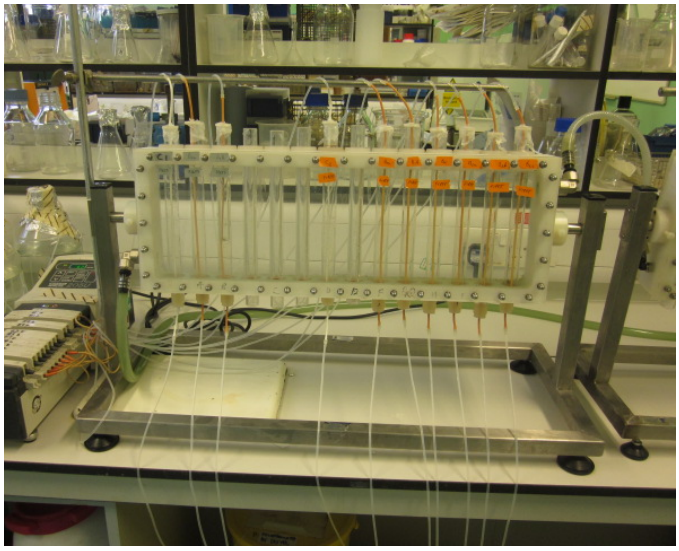


Fig 6. The in vitro dynamic model. Detail of apparatus including several control and antimicrobial-impregnated tubing into the glass cylinders.

2.2.8 Scanning Electronic Microscopy

The surface of the lumen of all the tubing was analysed using a JEOL 6060LV variable pressure scanning electron microscope. The impregnated tubing which passed the challenges was analysed after 42 days and the ones that failed were analysed when colonization was detected.

2.2.9 Statistical analysis

Optical density readings obtained in the biofilm formation assay were recorded as means +/- SD and the t test was used to compare the strain which produced the most biofilm F2653 with the others. A p value <0.05 was considered to indicate statistical significance.

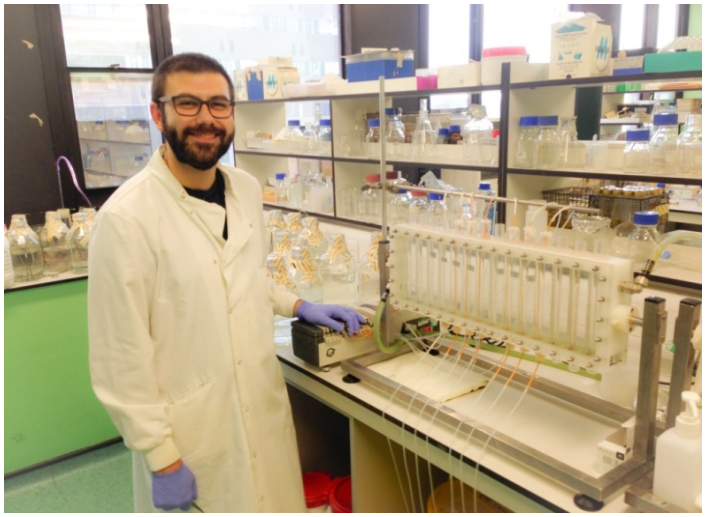


Fig 7. The doctoral candidate and the in vitro dynamic model for studying the activity of the new antimicrobial catheter against A. baumannii.

3. Funding and Grants

The doctoral candidate received the following grants and funding during his research:

1. Pre-doctoral research contract from Red Española de Investigación en Patología Infecciosa (REIPI).

2. Personal pre-doctoral grant from Institut d'Investigació Biomèdica de Bellvitge (IDIBELL).

3. Travel grants for UK research period, from the Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC) and the Societat Catalana de Malalties Infeccioses i Microbiologia Clínica (SCMIMC).

RESULTS

A. Hydrocephalus complicating community-acquired bacterial meningitis

A.1. Hydrocephalus in adults with C-ABM.

Aim 1. To evaluate occurrence, clinical characteristics and treatment of patients with hydrocephalus complicating C-ABM.

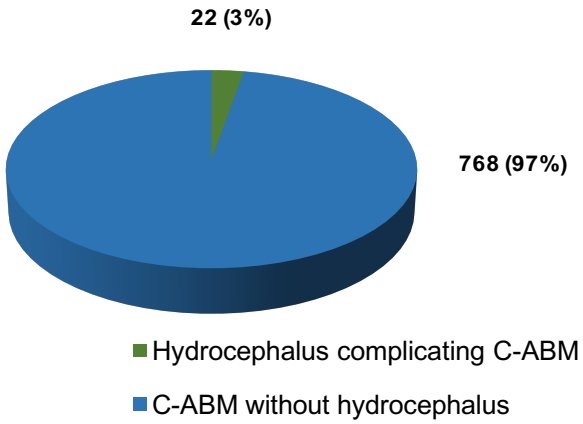
Aim 2. To measure the impact of complicating hydrocephalus on the outcome of patients with C-ABM.

Aim 3. To determine risk factors for the development of hydrocephalus complicating C-ABM.

Oral communication 1- *Hydrocephalus in adults with community acquired bacterial meningitis.* **Pelegrín I**, Verdaguer R, Ariza J, Fernández-Viladrich P, Cabellos C. XVI Congreso Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC). Bilbao, May 2012.

We collected all episodes of C-ABM between January 1977 and January 2011 and selected patients who developed hydrocephalus complicating C-ABM. Hydrocephalus was diagnosed in 22 of 790 (3%) episodes of C-ABM (Figure 8).

Fig 8. Frequency of hydrocephalus-complicating C-ABM



The most common causative agents were *Listeria monocytogenes* 7/22 (32%), *Streptococcus pneumoniae* 7/22 (32%) among the hydrocephalus C-ABM group (see Figure 9) and *Neisseria meningitidis* 310/ 790 (39%), *S. pneumoniae* 261/790 (33%), *L. monocytogenes* 56/790 (7%) among C-ABM patients without hydrocephalus (see Figure 10).

Fig 9. Aetiologies of 22 episodes of C-ABM who developed hydrocephalus

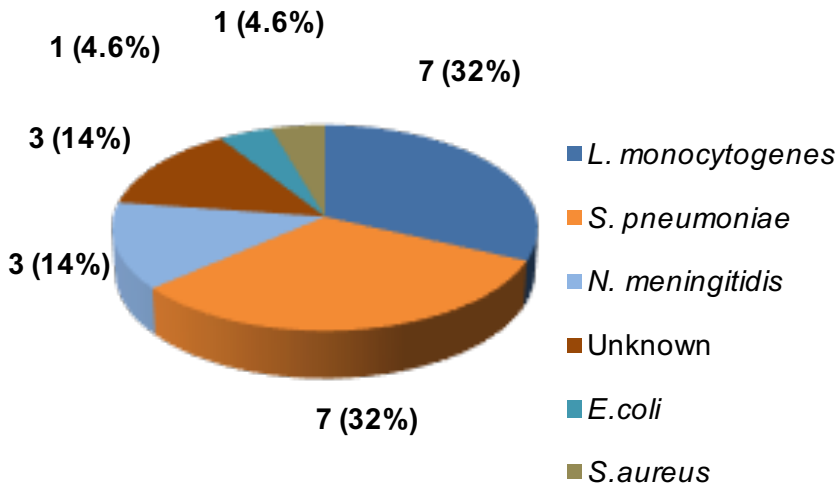
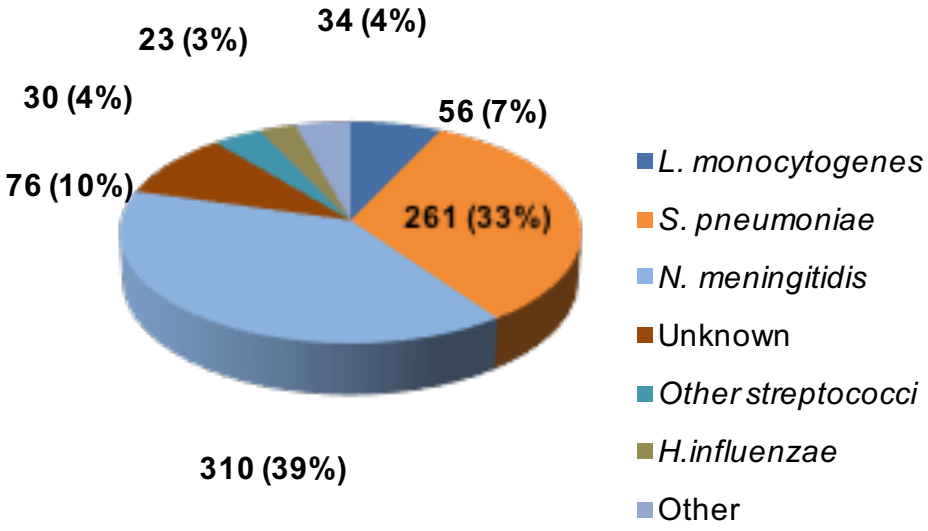


Fig 10. Aetiologies of 790 episodes of C-ABM



Clinical characteristics, outcome and treatment of 22 episodes which developed hydrocephalus complicating C-ABM are shown in Table 1.

Time to illness was > 48h in 14/22 (63%) in the hydrocephalus C-ABM group and 184/768 (24%) in the other group. Ten out of 22 (46%) patients were diagnosed at admission and 12/22 (54%) during hospital stay [median 6 days (IQR 3.5-11)]. Hydrocephalus was classified as communicanting in all cases.

Table 1. Epidemiology, clinical characteristics, treatment and outcome of 22 patients with hydrocephalus complicating C-ABM.

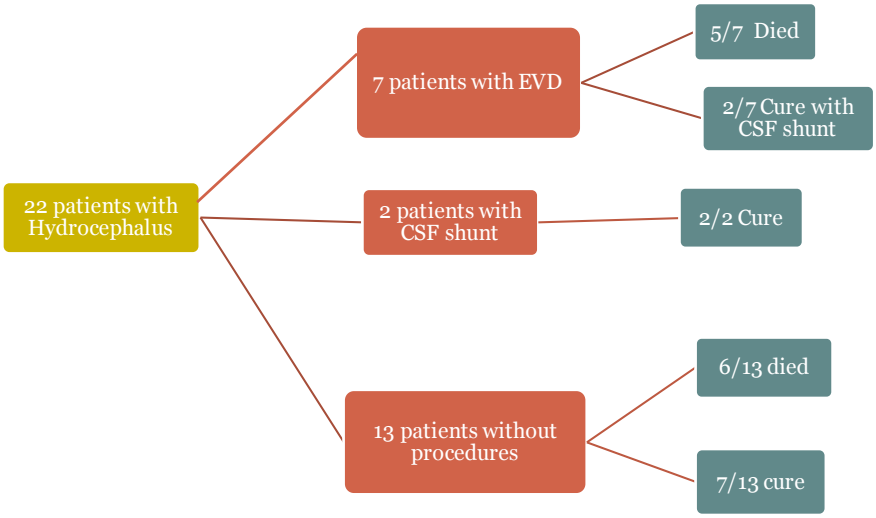
	N	%
Epidemiologic characteristics		
Sex (male)	13	59
Age (years) (μ) (R)	67	38-94
Underlying diseases	10	46
Signs and symptoms		
Time to illness (> 48h)	14	63
Fever	22	100
Neck stiffness	20	91
Altered mental status	19	86
Nausea/vomits	15	68
Headache	14	64
Microbiology		
CSF culture positive	16	73
Positive blood culture	13	68
Hydrocephalus diagnosis		
Admission	10	46
Evolution	12	54
Time to diagnosis (days) (Md, IQR)	6	3.5-11
Treatment of hydrocephalus		
EVD	7	32
VP shunt	4	18
Outcome		
ICU admission	8	36
Mortality	11	50
Neurologic death	9	41
Neurologic sequelae	6	55

Neurologic sequelae were present in six patients who survived. Four presented permanent hydrocephalus and needed a CSF shunt. Among them one developed epilepsy and another hemiparesis plus cranial nerve palsy. Of the other two who did not need CSF shunt, one presented hemiparesis and the other deafness.

Eleven out of 22 (50%) died, mostly of neurological causes 9/11 (82%). Two out of 11 (18%) died due to respiratory failure. Neurological causes of death were mostly related with hydrocephalus, although one patient died due to a concomitant epileptic status and the other due to a concomitant cerebral haemorrhage after an EVD placement.

Neurosurgical treatment, if performed, and outcome of the 22 patients who developed hydrocephalus complicating C-ABM are shown in Figure 11. Of note, mortality was higher in patients which required neurosurgical treatment 5/9 (56%) vs 6/13 (46%).

Figure 11. Neurosurgical treatment and outcome of 22 patients with hydrocephalus-complicating C-ABM.



Patients who developed hydrocephalus complicating C-ABM were compared to those who did not; table 2 shows the significant differences between the groups.

Table 2. Comparison between patients who developed hydrocephalus complicating C-ABM and those who did not.

	Hydrocephalus (n=22)	Without Hydrocephalus (n=768)	*p*
Age (years) (μ)	67	49	<0.001
Time to illness (>48h) (%)	64	24	<0.001
L. monocytogenes (%)	32	6	<0.001
Hemiparesis (%)	32	8	0.002
Seizures (%)	38	15	0.009
Cranial nerve palsy (%)	29	8	0.006
Hospital stay (days) (μ)	35	16	<0.001
Neurologic sequelae (%)	55	13	0.002
Mortality (%)	50	14	<0.001

Multivariate analysis of risk factors for development of hydrocephalus was performed: Age (OR 1.05, 95%CI: 1.02-10.81), time to illness > 48h (OR 4.29, 95%CI: 1.73-10.68) and *L. monocytogenes* (OR 2.8, 95%CI: 1.02-7.66) were independent risk factors for development of hydrocephalus.

Overall mortality and neurologic sequelae were higher in the hydrocephalus C-ABM group: 11/22 (50%) vs 108/768 (14%) (p<0.001) and 6/11 (55%) vs 89/660 (13%) respectively, as shown in Table 2.

Since 1987, use of dexamethasone as adjuvant treatment for C-ABM has been available at our centre. Although this drug has mostly been used in pneumococcal meningitis, some patients with other aetiologies have also received it. Here we compared patients who received it or did not receive it since 1987. Its use did not statistically influence the development of hydrocephalus in C-ABM. Among the 434 episodes of C-ABM recorded since 1987, 214 patients received dexamethasone, of whom four (1.9%) developed hydrocephalus; out of 220 patients who did not receive this drug, seven (3.2%) developed hydrocephalus (p=0.544).

In a subanalysis of pneumococcal meningitis, the effect of dexamethasone was not statistically significant but there was a trend towards fewer episodes complicated with hydrocephalus in the dexamethasone group. One hundred and seventy episodes of pneumococcal meningitis were recorded. Among 126 patients who received dexamethasone only two (1.6%) developed hydrocephalus, while out of 44 patients who did not receive this drug three (6.8%) developed hydrocephalus (p=0.110).

A.2 *L. monocytogenes* meningoencephalitis

Aim 1. To evaluate the efficacy of antibiotic and adjuvant therapy in LMME patients.

Aim 2. To analyse the risk factors for mortality and sequelae in LMME patients.

Article 1. *Listeria monocytogenes meningoencephalitis in adults: analysis of factors related to unfavourable outcome.* **Pelegrín I**, Moragas M, Suárez C, Ribera A, Verdaguer R, Martínez-Yelamos S, Rubio-Borrego F, Ariza J, Viladrich PF, Cabellos C. Infection. 2014; 42: 817-27.

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CLINICAL AND EPIDEMIOLOGICAL STUDY

Listeria monocytogenes meningoencephalitis in adults: analysis of factors related to unfavourable outcome

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Abstract
Purpose To analyse the short-term outcome in patients with *Listeria monocytogenes* meningoencephalitis (LMME) to improve management and outcome.
Methods Observational study with adult patients with LMME between 1977 and 2009 at a tertiary hospital in Barcelona, Spain. Parameters that predicted outcome were assessed with univariate and logistic regression analysis.
Results Of 59 cases of LMME, 28 occurred in the last decade. Since 1987, a new protocol has been used and 29/45 patients (64 %) treated since then received adjuvant dexamethasone. In patients who received this treatment there was a trend towards fewer neurological sequelae (5 vs 33 %; $p = 0.052$). Antiseizure prophylaxis with phenytoin was administered in 13/45 (28 %) patients. Seizures occurred in 7/45 (16 %) patients, all in the group who did not receive phenytoin. Hydrocephalus presented in 8/59 (14 %). It was never present at admission and five patients needed neurosurgical procedures. Sequelae after 3 months were present in 8/45 (18 %), mostly cranial nerve palsy. Rhombencephalitis (RE) was related to the presence of neurologic sequelae (OR: 20.4, 95 % CI: 1.76–236). Overall mortality was 14/59 (24 %), 9/59 (15 %) due to neurological causes related to hydrocephalus or seizures. Mortality was defined as early in 36 % and late in 64 %. In the multivariate analysis, independent risk factors for mortality were presence of hydrocephalus (OR: 17.8, 95 % CI: 2.753–114) and inappropriate empirical antibiotic therapy (OR: 6.5, 95 % CI: 1.201–35).
Conclusions Outcome of LMME may be improved by appropriate empirical antibiotic therapy, suspicion and careful management of hydrocephalus. Use of adjuvant dexamethasone or phenytoin in a subgroup of these patients might have a benefit.

Keywords Meningitis · *Listeria monocytogenes* · Outcome · Hydrocephalus

Introduction

In recent years, an increase in the rate of *Listeria monocytogenes* meningoencephalitis (LMME) has been reported worldwide, with an estimated annual incidence in developed countries between 0.05 and 0.2 cases per 100,000 population [1, 2]. LMME has become the third most common pathogen causing community-acquired bacterial meningitis (C-ABM) in adults [3]. Among the possible causes of this scenario is the higher prevalence of susceptible populations such as elderly patients and patients with impaired cellular immunity, well-known predisposing factors for invasive listeriosis [4–6].

This observation is of special concern, because mortality rates ranging from 17 % to more than 30 % have repeatedly been reported in LMME [3, 7–9]. A recent study performed to clarify the role of dexamethasone in LMME

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showed a high rate of unfavourable outcome (61 %) and mortality (36 %) [10].

The latest research into LMME has focused on the analysis of an optimal choice of antibiotic therapy, and some authors have suggested that the addition of aminoglycosides may be deleterious [7, 9, 11]. While the high mortality rates accompanying this disease may be favoured above all by the frequently poor underlying condition of the host, the specific role of other factors influencing the prognosis of these patients is not well defined. Indeed, few data are currently available regarding the relevance of hydrocephalus, a commonly reported complication (15 % [12]), and of other neurological findings, or regarding the possible benefits of prophylaxis with dexamethasone or anticonvulsants.

We performed a detailed analysis of early and late mortality and sequelae in 59 patients with LMME included in an observational study over a long period (1977–2009). We focused on the differences between two clinical forms of LMME—meningitis and rhombencephalitis (RE)—the course of hydrocephalus and its treatment, and the possible role of dexamethasone or anticonvulsants as prophylaxis in LMME. We aim to analyse these prognostic factors and contribute to improve the outcome of LMME.

Patients and methods

Setting and study population

The Hospital Universitari de Bellvitge is a tertiary teaching hospital for adult patients (≥16 years old) in Barcelona, Spain. Since 1977, all cases of C-ABM have been prospectively recorded. We retrospectively identified all cases of LMME among C-ABM between 1977 and 2009, and also included cases presenting as rhombencephalitis. The number of admissions per year in our hospital increased from 18,963 in 1977 to 28,577 in 2009.

This study was approved by the Clinical Research Ethics Committee of our institution.

Clinical and microbiological studies

An initial lumbar puncture and blood cultures were performed in all cases of suspected bacterial meningitis. CSF samples were submitted for Gram stain, bacterial cultures, and cytochemical tests. After centrifugation of CSF specimens, the resulting sediment was used to prepare smears for microscopic examination and to inoculate blood and chocolate agar plates and thioglycolate broth. Microbiological identification was performed according to standard methods [13]. Antibiotic susceptibilities were determined by disk-diffusion, complemented, if necessary, by determination of MICs and minimum bactericidal concentrations [14]. All patients were evaluated daily during admission. After discharge they were assessed at the outpatient clinic within the following 4 weeks and 3 months after the episode.

Definitions

LMME was diagnosed in patients with compatible clinical findings suggestive of meningitis or rhombencephalitis and positive CSF culture for *Lm* and/or positive blood culture for *Lm* and CSF pleocytosis (> 5cells/mm3). The diagnosis of RE required clinical evidence of brainstem and/or cerebellum involvement (ataxia or cranial nerve involvement, plus spinothalamic tract, corticospinal tract, or posterior columna abnormalities) or a conclusive neuroimaging study. Time to presentation was defined as the time from onset of symptoms to the first dose of an appropriate antibiotic therapy. Patients who presented a time to presentation longer than 2 days were defined as having late presentation and those with a time to presentation longer than 4 days were defined as very late presentation. "Underlying conditions" were defined, if at least one of the following were present in the medical record, as: diabetes mellitus, hepatic cirrhosis, solid and haematologic neoplasm, chronic corticosteroid therapy and other immunosuppression comorbidities. Corticosteroid therapy was defined as ≥5 mg/24 h of prednisone or an equivalent dose of another corticosteroid. Immunosuppression was considered if other illnesses or treatments that cause immunosuppression were present. Cranial computed tomography (CT) was not routinely performed. Hydrocephalus was diagnosed on the basis of clinical symptoms and measurement of Evan's index in CT [15, 16]. Presence of seizures was defined by the criteria of the "International Classification of Seizures" and "International Classification of Epilepsies and Epilepsy syndromes". Impairment of renal function was defined as a doubling in the serum creatinine level or a level of >150 umol/L. Neurologic sequelae were evaluated at the outpatient clinic and diagnosed if they were present 3 months after discharge.

Treatment

Since 1987, all patients at our institution with suspected pneumococcal meningitis and/or patients with meningitis with intracranial hypertension (>30 cm H_2O) in the emergency room have been routinely treated with dexamethasone 4 mg/6 h for 48 h, eight doses in total, beginning 10–15 min before antibiotic therapy with a doubled first dose. Antiseizure prophylaxis with phenytoin, loading dose of 18 mg/Kg, followed 24 h later by a maintenance dose (2 mg/Kg/8 h) during 10 days, immediately after antibiotic therapy. Since 2003, after publication of results

of a European controlled trial in C-ABM [17], adjuvant treatment with dexamethasone has been administered in most cases with suspicion of bacterial meningitis at our centre. For this reason, some patients with LMME received this treatment.

Intravenous administration of penicillin, ampicillin, vancomycin, a carbapenem or cotrimoxazole was considered adequate empirical treatment. The definitive therapy choice was ampicillin ± aminoglycosides, usually gentamicin 3–5 mg/Kg/day iv, if possible, as recommended.

Causes of death

Two experienced infectious diseases consultants reviewed the medical records to confirm the most likely cause of death. Mortality was defined during hospitalization and classified as early if it occurred in the first week after admission and late if it occurred more than 1 week after admission.

Statistical analysis

For descriptive analysis of episodes of LMME, categorical data were compared using the Chi-square test or Fisher's exact test, and continuous data with the *t* test or Mann–Whitney *U* test, as appropriate. Specific comparative analysis was performed on patients presenting either as RE or meningitis. Also, to evaluate the role of adjuvant dexamethasone, we compared patients who receive this treatment since 1987 with patients who did not receive it.

To identify independent predictors of mortality of patients with LMME, multivariate logistic regression analysis was performed. For this, variables with a p value <0.30 in the univariate analysis were included in a stepwise backward selection process, using values of PIN = 0.05 and POUT = 0.10. According to a pre-agreed analytical plan, the initial model also included the following parameters, regardless of the p value in the univariate analysis: sex, age, the presence of underlying diseases, and the definite antimicrobial treatment. External CSF ventricular catheter variable was excluded in the model due to collinearity with hydrocephalus. The best model was chosen based on the likelihood ratios.

Furthermore, we performed separated univariate analysis for identifying parameters associated with the following outcomes: development of hydrocephalus, presence of seizures and development of sequelae.

A Mantel–Haenszel test for trends was performed to evaluate trends of LMME during the study period.

All statistical tests were two-tailed, and p values of <0.05 were considered statistically significant. All the analyses were conducted using SPSS software, version 15.0.

Results

Epidemiology and clinical characteristics

Between 1977 and 2009, 808 episodes of C-ABM were recorded. The most common aetiologies were *Neisseria meningitidis (*311, 38 %), *Streptococcus pneumoniae (*247, 31 %), *Listeria monocytogenes* (59, 7 %) and *Haemophilus influenzae* (21, 3 %).

In the last period (1999–2009), 206 episodes of C-ABM were identified. *S. pneumoniae* was the most common pathogen (88, 43 %), followed by *N. meningitidis* (45, 22 %). *L. monocytogenes* increased markedly, to 28 episodes (14 %). In the previous periods, we identified 15 episodes (7 %) of LMME from 1988 to 1998 and 16 episodes (4 %) from 1977 to 1987 ($p < 0.001$).

A similar increase was observed in the number of LMME per 1,000 admissions, which rose from 0.73 (1977–1998) to 1.02 (1999–2009).

Among the fifty-nine patients with LMME recorded, 53 (90 %) patients presented at least one underlying condition and/or were over the age of 50. Six (10 %) patients were young adults (range of age 30–48 years) without any underlying conditions. Symptoms were present for >2 -days in 30 (51 %) patients and for >96 h in 13 (22 %) (Table 1).

The time to presentation was longer among the 15 (25 %) patients with focal signs compared to the 44 (75 %) patients without. Patients presenting focal signs at admission had a higher frequency of time to presentation longer than 4 days (7/15, 46 %) compared to the patients without them (6/44, 13 %) ($p = 0.013$).

Laboratory and microbiological data

CSF culture yielded *L. monocytogenes* in 48/59 patients (83 %) but only three (6 %) had positive Gram stain. Blood cultures were positive in 34/53 (64 %). Serogroup 4 was the most frequent group, accounting for 32/35 (91 %); the other three were serogroup 1.

Treatment and outcome

Empirical antibiotic therapy was inappropriate in nine patients (15 %). Fifteen (25 %) patients received ampicillin alone as definitive treatment and 39 (66 %) received ampicillin plus aminoglycosides. Three (8 %) patients received cotrimoxazole 15–20 mg/Kg/day of trimetoprim due to allergy to betalactams. In one of these patients vancomycin was the initial definitive treatment but microbiological failure was observed after 5 days. Two (3 %) did not received any treatment. Median duration of treatment was 21 days (IQR 14–22.5). Nine patients

Table 1 General characteristics of 59 patients with LMME and comparison between deceased and survivors

	Total ($n = 59$)	Patients who died ($n = 14$)	Patients who survived ($n = 45$)	p value
Age (years), M (Range)	64 (29–94)	69 (48–94)	63 (29–83)	0.038
Male sex	41/59 (70 %)	10 (71 %)	31 (69 %)	1
Underlying conditions				
Diabetes mellitus	14/59 (24 %)	5 (36 %)	9 (20 %)	0.227
Chronic corticosteroid therapy	14/59 (24 %)	5 (36 %)	9 (20 %)	0.227
Liver cirrhosis	6/59 (10 %)	1 (7 %)	5 (11 %)	1
Solid Neoplasm	4/59 (7 %)	2 (14 %)	2 (4 %)	0.236
Haematologic neoplasm	3/59 (5 %)	2 (14 %)	1 (2 %)	0.137
Immunosuppression[a]	5/59 (8 %)	2 (14 %)	3 (7 %)	0.339
Any underlying condition listed above	23/59 (39 %)	8 (57 %)	15 (33 %)	0.111
Clinical features				
Fever $\geq$ 38 °C	54/59 (92 %)	12 (92 %)	42 (93 %)	1
Meningeal signs	46/59 (78 %)	10 (83 %)	36 (84 %)	1
Altered mental status	44/59 (75 %)	11 (77 %)	32 (71 %)	0.738
Headache	42/59 (72 %)	9 (75 %)	33 (75 %)	1
Hemiparesis	5/59 (9 %)	1 (7 %)	4 (9 %)	1
Cranial Nerve Palsy	12/59 (20 %)	5 (36 %)	7 (16 %)	0.102
Focal signs[b]	15/59 (25 %)	5 (36 %)	10 (22 %)	0.316
Seizures	7/59 (12 %)	3 (21 %)	4 (9 %)	0.340
Late presentation[c]	30/59 (51 %)	9 (65 %)	21 (47 %)	0.249
Very late presentation[d]	13/59 (22 %)	6 (43 %)	7 (16 %)	0.06
Time to presentation [d], median (IQR)	3 (1–4)	3.5 (1–6)	3 (1–4)	0.221
Microbiological findings				
Gram stain: Gram-positive rods	3/54 (6 %)	0 (0 %)	3 (7 %)	0.435
Positive CSF[e] culture	48/59 (81 %)	13 (93 %)	35 (78 %)	0.438
Positive blood cultures	34/53 (64 %)	5 (36 %)	29 (64 %)	0.057
CSF characteristics				
Opening pressure [mmH20], Md (IQR)	260 (172–330)	160 (118–292)	265 (215–330)	0.127
WBC count (cells/µl), Md (IQR)	400 (160–620)	340 (105–2,228)	416 (173–566)	0.555
Neutrophil (%), Md (IQR)	56 (25–75)	66 (30–87)	50 (25–70)	0.203
Protein level (>1 g/L)	47/55 (85 %)	11 (92 %)	36 (84 %)	0.670
Hypoglycorrhachia (<40 mg/dL)	33/54 (61 %)	7 (50 %)	26 (58 %)	0.655
Treatment				
Inappropriate empirical treatment	9/59 (15 %)	5 (36 %)	4 (9 %)	0.027
Ampicillin	15/59 (25 %)	2 (14 %)	13 (29 %)	
Ampicillin + AG[f]	39/59 (66 %)	8 (57 %)	31 (69 %)	0.708
Duration, median, IQR (days)	21 (14–23)	–	–	–
Use of dexamethasone	30/59 (51 %)	9 (64 %)	21 (47 %)	0.249
Antiseizure prophylaxis	13 (22 %)	4 (29 %)	9 (20 %)	0.502
Outcome				
Cure	45/59 (76 %)	–	–	–
Death	14/59 (24 %)	–	–	–
Neurologic	9/59 (15 %)			
Systemic	5/59 (8 %)			
Sequelae	8/45 (18 %)	–	–	–
Complications				
Renal impairment	9/59 (15 %)	5 (36 %)	4 (9 %)	0.042

Table 1 continued

	Total ($n = 59$)	Patients who died ($n = 14$)	Patients who survived ($n = 45$)	p value
Hydrocephalus	8/59 (14 %)	6 (43 %)	2 (4 %)	0.001
External ventricular catheter	5/8 (63 %)	4 (29 %)	1 (2 %)	0.002

Data are proportion of patients, unless otherwise indicated

[a] Immunosuppression: chronic renal impairment function ($n = 1$), systemic lupus erythematosus ($n = 1$), chronic hepatitis ($n = 1$), multiple myeloma ($n = 1$) and AIDS ($n = 1$). The HIV + patient presented a CD4 cell count of 72/mm^3 and did not take prophylaxis with cotrimoxazole

[b] Focal signs: hemiparesis or cranial nerve palsy

[c] Late presentation >2 days

[d] Very late presentation >4 days

[e] CSF: cerebrospinal fluid

[f] AG: aminoglycosides

suffered renal impairment as a complication during hospitalization: 3/39 (8 %) receiving aminoglycosides and 4/15 (27 %) of patients receiving ampicillin alone. ($p = 0.008$).

Since 1987, 29 out of 45 patients (64 %) received adjuvant dexamethasone. Patients who received dexamethasone tend to present more fever at admission than those who had not (97 vs 75 %, $p = 0.07$), and a higher median of number of cells in the CSF (483 vs 219 cells, $p = 0.081$) (Table 2). No significant differences in mortality or major side effects were recorded in the two groups, but there was a trend towards fewer neurologic sequelae in the dexamethasone group (1/20 5 % vs 4/12 33 %, $p = 0.052$).

Antiseizure prophylaxis with phenytoin was administered in 13 of 45 (28 %) patients since 1987. Seizures occurred in seven of 45 patients (16 %): four pre-hospital and three in-hospital (none of whom had received antiseizure prophylaxis) [0/13 (0 %) vs 3/28 (10 %), $p > 0.05$]. Patients who presented seizures were older [70 (69–79) vs 63 (56–71), $p = 0.017$], more frequently presented diabetes mellitus [4/7 (57 %) vs 10/52 (19 %), $p = 0.048$], and coma at admission [2/7 (29 %) vs 1/52 (2 %), $p = 0.035$]. These patients showed a trend towards higher neurologic mortality [3/7 (43 %) vs 6/52 (12 %), $p = 0.064$].

Hydrocephalus was recorded during hospitalization in 8 out of 59 cases (14 %). Among patients with symptoms for >4 days, hydrocephalus showed a trend to be more frequent, 4/13 (31 %), compared to those who had a time to presentation less or equal to 4 days 4/46 (9 %) ($p = 0.062$). A possible association was observed between time to presentation and frequency of hydrocephalus: patients with hydrocephalus showed a trend towards a longer median time to presentation than patients without hydrocephalus [4.5 (2–8 IQR) vs 3 (1–4 IQR) days, respectively, $p = 0.077$]. In 5 of 8 patients, CT scan was performed at admission and did not show intracranial abnormalities, so hydrocephalus was not diagnosed at admission. The median time from admission to detection of hydrocephalus was 6 days (range 2–30 days). Patients with hydrocephalus presented no differences in age (69 vs 63 years old, $p = 0.318$) and presented more focal signs at admission [5/8 (63 %) vs 10/51 (20 %), $p = 0.02$] than those who did not present it. During admission, five patients needed placement of external ventricular catheter and one definitive CSF shunt. Patients with hydrocephalus presented a worse outcome: greater need of mechanical ventilation [5/8 (60 %) vs 10/51 (20 %), $p = 0.007$), and higher overall [6/8 (75 %) vs 8/51 (16 %), $p = 0.001$] and neurological [6/8 (75 %) vs 3/51 (6 %), $p < 0.001$], mortality, occurring after a median time of 23 (IQR 13–50) days.

No relapses were recorded. Sequelae were present in eight patients, 18 % of those patients who survived, mainly cranial nerve palsy. They were mostly found in patients with focal disease at admission (Table 3) and in those with rhombencephalitis (OR: 20.4, 95 % CI 1.76–236,437). Adjuvant treatment with dexamethasone was a protective factor for development of sequelae (OR: 0.105, 95 % CI 0.01–1.095).

Eleven of the 59 episodes were recorded as rhombencephalitis. Patients with rhombencephalitis showed a trend to present less altered mental status (45 vs 79 %, $p = 0.054$), presented more late onset (82 vs 44 %, $p = 0.023$) and more sequelae (63 vs 8 %; $p = 0.002$) than patients with meningitis (Table 4).

Analysis of mortality

Overall mortality was 24 % ($n = 14$). Nine patients died between 1999 and 2009 (32 %), and five between 1977 and 1998 (16 %) ($p = 0.149$).

Risk factors for mortality

Risk factors for mortality in the univariate analysis included age ($p = 0.038$), inappropriate empirical therapy

Table 2 Comparison between LMME patients who receive adjuvant treatment with dexamethasone and those who did not receive it since 1987

	Patients who did not receive prophylaxis with dexamethasone $n = 16$	Patients who received prophylaxis with dexamethasone $n = 29$	p value
Age (years), M (Range)	63 (58–72)	69 (62–75)	0.196
Male sex	14 (87 %)	20 (69 %)	0.279
Underlying conditions			
Liver cirrhosis	2 (13 %)	1 (3 %)	0.285
Haematological neoplasm	0 (0 %)	3 (10 %)	0.542
Diabetes mellitus	6 (38 %)	6 (21 %)	0.056
Chronic corticosteroid therapy	1 (6 %)	9 (31 %)	0.249
Immunosuppression	2 (13 %)	4 (14 %)	1
Any underlying condition listed above	7 (44 %)	12 (41 %)	1
Clinical features			
Fever	12 (75 %)	28 (97 %)	0.07
Headache	11 (69 %)	21 (72 %)	0.654
Meningeal signs	10 (63 %)	25 (86 %)	0.104
Altered mental status	10 (63 %)	23 (79 %)	0.222
Hemiparesis	2 (13 %)	1 (3 %)	0.285
Cranial nerve palsy	6 (36 %)	6 (21 %)	0.296
Focal signs	6 (38 %)	7 (24 %)	0.494
Seizures	1 (6 %)	6 (21 %)	0.049
Meningitis	11 (69 %)	23 (79 %)	0.43
Rhombencephalitis	5 (31 %)	6 (21 %)	0.43
Late presentation	8 (50 %)	15 (52 %)	0.912
Days to fever below 38 °C, Md (IQR)	5 (2–7)	2 (1–5)	0.065
Laboratory characteristics			
Opening pressure (water mmH20), Md (IQR)	24 (16–30)	26 (18–33)	0.553
WBC count (cells/μl), Md (IQR)	219 (98–517)	483 (212–784)	0.081
Protein level (>1 g/L)	12 (75 %)	27 (93 %)	0.223
Hypoglycorrhachia (<40 mg/dL)	8 (50 %)	17 (59 %)	0.375
Positive blood cultures	7 (44 %)	18 (62 %)	0.236
Positive CSF culture	13 (81 %)	24 (83 %)	0.699
Treatment			
Empirical inappropriate treatment	3 (21 %)	8 (28 %)	0.686
Ampicillin	4 (25 %)	5 (17 %)	–
Ampicillin + AG	10 (71 %)	22 (82 %)	0.692
Antiseizure prophylaxis	0 (0 %)	13 (45 %)	0.002
Outcome			
Death	4 (25 %)	9 (31 %)	0.743
Neurological death	3 (19 %)	8 (28 %)	0.72
Sequelae	4 (33 %)	1 (5 %)	0.052
Hydrocephalus	2 (13 %)	5 (17 %)	0.674
Hospital stay, Md (days)	21 (15–37)	23 (20–30)	0.704
Complications			
Gastrointestinal bleeding	1 (6 %)	4 (14 %)	0.31
Renal impairment	3 (19 %)	4 (14 %)	0.686

Table 3 LMME patients who presented focal signs at admission or showed neurologic sequelae

Case	Sex/age	Year	Clinical form	Time to presentation (days)	Focal signs at admission	H	DXM	Mortality	Sequelae at 3 months
1	M/56	1978	ME	3	No/Hemip	No	No	No	Hemip/Coma
2	M/53	1984	ME	2	No/Hemip	Yes	Yes	No	CNP not specified/Hemip/H-shunt
3	M/62	1994	RE	4	VII/IX	No	Yes	No	VII/IX
4	M/65	1995	RE	60	I/VI/IX/X/XI/XII	Yes	No	Yes	–
5	F/61	1996	RE	4	V	No	Yes	No	No
6	M/61	1998	ME	6	VII/Hemip	No	No	Yes	–
7	M/34	1999	RE	5	VI	No	Yes	No	No
8	M/79	2000	ME	9	VII	No	Yes	Yes	–
9	F/48	2001	RE	3	VI	Yes	Yes	Yes	–
10	M/59	2002	RE	4	III/VI/VII	No	No	No	III/VI/VII
11	F/74	2004	RE	1	VI/VII/IX	No	No	No	VI/VII/IX
12	M/56	2005	RE	8	V/IX/X	No	No	No	V/IX/X
13	F/70	2007	RE	3	No/Hemip	No	Yes	No	No
14	F/53	2007	RE	7	VI/VII/Hemip	No	No	No	VI/VII/Hemip
15	F/84	2009	RE	5	VI	Yes	Yes	Yes	–
16*	F/63	1984	ME	4.5	No	No	No	No	Tetraparesis

M male, *F* female, *M* meningitis, *RE* rhombencephalitis, *Hemip* hemiparesis, *DXM* dexamethasone, *H* hydrocephalus, *CNP* cranial nerve palsy

* A patient who presented no focal signs at admission but developed in the first days after admission neurological impairment and presented tetraparesis

($p = 0.027$), renal impairment ($p = 0.042$), hydrocephalus ($p = 0.001$) and placement of an external ventricular CSF catheter ($p = 0.002$). No statistically significant difference was seen in mortality between choice of treatment, time from onset of symptoms to first dose of appropriate antibiotic therapy, presence of seizures or rhombencephalitis and use of adjuvant dexamethasone or antiseizure prophylaxis (Table 1).

In the multivariate analysis, independent risk factors for mortality were presence of hydrocephalus (OR: 17.8, 95 % CI 2.753–114) and inappropriate empirical antibiotic therapy (OR: 6.5, 95 % CI 1.201–35).

Causes of death

Specific clinical characteristics of patients who died are shown in Table 5. Mortality was defined as early in five of 14 (36 %) patients with a median time from admission to death of 4 days (range 3–6 days), and late in the other nine (64 %) with a median time from admission to death of 25 days (range 13–79 days). Nine of 14 patients (64 %) died due to neurological complications, and the other five (36 %) due to systemic complications. Necropsy was performed in only three cases. Pathological findings are shown in Table 5.

Discussion

Our findings are in agreement with the recent increase in LMME reported by other authors worldwide [3, 7, 9, 18, 19] that place *L. monocytogenes* as the third most common cause of C-ABM in adults, following pneumococcal and meningococcal meningitis. In fact, its incidence increased from 0.73 cases/1,000 admissions in our first period (1977–1998) to 1.02 cases/1000 admissions in the last decade (1999–2009).

Overall mortality in our series was high (24 %), in the middle of the reported range in recent cohort studies (17–36 %) [7–10]. Time and causes of death are issues that are not well defined in the literature. Mortality was defined as early in a third of our patients, due to neurological causes (60 %), mostly seizures, and systemic complications (40 %), and late in the other two-thirds, due to neurological complications, mainly caused by hydrocephalus.

Inappropriate empirical antibiotic therapy and hydrocephalus were the main independent prognostic factors identified for mortality. This is a relevant finding which has not described previously in cohorts of LMME patients, because these factors may potentially be modified. While total time of presentation was not clearly associated with mortality, inappropriate empirical antibiotic choice was especially deleterious in our patients who presented early mortality (60 %). Thus, physicians should always consider adding ampicillin to cephalosporin when C-ABM is diagnosed in the emergency room without aetiological confirmation in patients above 50 years of age, as recommended in the IDSA guidelines [20]. Furthermore, we recommend adding ampicillin in patients of all ages with suspected C-ABM of unknown focus and without petechial rash, especially in patients with immunosuppression.

Table 4 Comparison between cases of *L. monocytogenes* meningitis and rhombencephalitis

	Meningitis ($n = 48$)	Rhombencephalitis ($n = 11$)	p value
Age (years), M (range)	64 (12.9)	61 (13.4)	0.406
Male sex	36 (75 %)	5 (46 %)	0.064
Underlying conditions			
Diabetes mellitus	11 (23 %)	3 (27 %)	0.712
Corticosteroids	12 (25 %)	2 (18 %)	1
Liver cirrhosis	6 (12 %)	0 (0 %)	0.582
Solid neoplasm	4 (8 %)	0 (0 %)	1
Haematologic neoplasm	2 (4 %)	1 (9 %)	0.468
Immunosuppression	3 (6 %)	3 (27 %)	0.072
Clinical features			
Fever	45 (94 %)	9 (82 %)	0.541
Meningeal signs	39 (81 %)	7 (64 %)	0.340
Altered mental status	38 (79 %)	5 (45 %)	0.054
Headache	35 (73 %)	7 (64 %)	0.439
Seizures	5 (10 %)	1 (9 %)	1
Late presentation	21 (44 %)	9 (82 %)	0.023
Time to presentation [d], median (IQR)	2 (1–4)	4 (3–7)	0.01
Microbiological findings			
Positive CSF culture	41 (85 %)	7 (64 %)	0.153
Positive blood culture	28/43 (65 %)	6/10 (60 %)	0.819
Duration of treatment (Days) Md (IQR)	20 (14–22)	21.5 (21–39)	0.03
Outcome			
Hydrocephalus	5/48 (10 %)	3/11 (27 %)	0.16
Death	11/48 (23 %)	3/11 (27 %)	0.712
Sequelae	3/37 (8 %)	5/8 (63 %)	0.002

Communicating hydrocephalus was a frequent complication of LMME in our series (14 %). Other authors have previously reported this observation [12], but its global relevance in the prognosis of LMME has not been sufficiently emphasized. This complication may be found in both clinical forms of LMME, meningitis and rhombencephalitis, and its presence shows a possible relationship with the time to presentation since the frequency of hydrocephalus among our patients with symptoms for >4 days was higher than 30 %. It is not often diagnosed at admission, as CT scan appears normal, and its detection in our patients was delayed for a median of 6 days after admission. While we could not modify the long pre-admission period of the disease, suspicion and careful management of hydrocephalus might influence the clinical prognosis of a defined group of LMME patients: those with symptoms for >4 days, often associated with focal signs at admission, and especially if consciousness is not recovered after 24 h of appropriate treatment or if it declines during evolution. We cannot corroborate that hydrocephalus may be the direct cause of death itself but a result of a more severe infection. However, when hydrocephalus is diagnosed, early indication of placement of external ventricular drainage should be carefully discussed with the neurosurgery team, in an attempt to improve the mortality rate.

Other potentially relevant factors not identified as being clearly associated with LMME patient outcome, such as definitive antimicrobial treatment choice, adjuvant therapy, and seizures also merit discussion.

We found no differences in mortality between the group treated with high doses of ampicillin alone for 21 days (13 %) and the group treated with ampicillin plus aminoglycosides (21 %). Combination therapy has been established as the recommended treatment for LMME, based in experimental in vitro [21] and in vivo studies [22], case report series [23], expert opinions [5] and guidelines [20]. However, some authors have suggested higher mortality among patients treated with aminoglycosides, arguing that this treatment should be avoided due to its toxicity and an unclear beneficial effect [7, 9, 11]. Our data do not provide sufficient evidence for comparison, but they do not appear to support the notion of a poorer prognosis of patients receiving aminoglycosides recently described in LMME patients. In the absence of results from randomized clinical trials, we think that a short course of 5–7 days of

Table 5 Description of LMME patients who died

Case	Sex/ Age	Year	Underlying conditions	Days to death	DXM	PHT	Inappropriate empirical Tx	Seizure/ Time	RI	H	CT admission/ evolution	Days to H	EVD	Necropsy	Cause of death
1	M/53	1983	LC/steroids	5	No	No	Yes	No/–	Yes	No	–/–	–	No	No	Persistence of meningeal/brain inflammation
2	M/65	1987	SN/steroids	6	Yes	No	Yes	No/–	No	No	N/–	–	No	No	Bronchoaspiration after neurological recovery
3	M/63	1990	HN/CRF/DM	4	Yes	No	No	Yes/ 24 h	Yes	No	–/–	–	No	No	Seizures although antiepileptic drugs
4	M/65	1995	–	31	No	No	Yes	No	No	Yes	N/H and SAH	30	No	Yes[a]	SAH after neurological recovery
5	M/61	1998	SN/DM	17	No	No	No	No	No	Yes	N/H	5	Yes	Yes[b]	Persistence of meningeal/brain inflammation[d]
6	M/79	2000	DM	3	Yes	No	Yes	Yes/ BTx	Yes	No	N/N	–	No	No	Seizures although antiepileptic drugs
7	F/48	2001	LES/DM/ steroids	50	Yes	Yes	No	No	No	Yes	N/H	2	Yes	No	H leading a vegetative state
8	M/73	2004	–	3	No	No	No	No	No	No	–/–	–	No	No	AMI after neurological recovery
9	M/84	2004	DM	15	No	No	No	Yes/4d	No	No	SDH/SDH	–	No	No	Seizures although antiepileptic drugs
10	F/80	2007	HN	23	Yes	No	No	No	Yes	No	N/–	–	No	No	Respiratory failure after neurological recovery
11	F/94	2008	–	13	Yes	Yes	Yes	No	Yes	Yes	–/H	5	No	No	Acute Renal failure and Acute cardiac failure
12	M/80	2008	steroids	25	Yes	Yes	No	No	No	Yes	N/H	7	Yes	No	H leading a vegetative state
13	M/61	2008	steroids	79	Yes	No	No	No	No	No	N/–	–	No	Yes[c]	Respiratory failure after neurological recovery
14	F/84	2009	–	20	Yes	Yes	No	No	No	Yes	–/H	7	Yes	No	H and ICH due to EVD

M male, *F* female, *SN* solid neoplasia, *LC* liver cirrhosis, *HN* haematological neoplasia, *CRF* chronic renal failure, *DM* diabetes mellitus, *SLE* systemic lupus erythematosus, *DXM* dexamethasone, *PHT* phenytoin, *Tx* antibiotic therapy, *BT* before antibiotic therapy, *RI* renal impairment, *H* hydrocephalus, *CT* cranial tomography, *N* normal, *SDH* subdural haemorrhage, *SAH* subarachnoid haemorrhage, *EVD* external ventricular drain, *AMI* acute myocardial infarction, *ICH* intracerebral haemorrhage, *IH* intracranial hypertension

[a] Subarachnoid haemorrhage with uncal and cerebellar tonsils herniation. Purulent meningitis in a subacute phase

[b] Purulent meningitis with purulent periventricular necrosis in lateral, III and IV ventricles

[c] Pulmonary bilateral oedema and patchy bilateral areas of consolidation. No infectious signs in the meninges and brain

[d] In one of these patients vancomycin was the initial definitive treatment but microbiological failure was seen after 5 days

aminoglycosides added to ampicillin may provide a sufficient synergistic effect without causing relevant side effects.

In a European controlled trial in C-ABM [17], adjuvant treatment with dexamethasone was associated with a reduction in mortality, especially in *S. pneumoniae* (34 to 14 %). However, in that study immunocompromised patients were not included and the role of dexamethasone in *L. monocytogenes* meningitis could not be well defined. The same authors have since performed another study to evaluate the role of dexamethasone, and recommend its withdrawal after isolation of *L. monocytogenes*, as no beneficial effect was found [10]. While the use of dexamethasone was safe we found no influence on mortality like Brouwer et al. Regarding the possible benefit of dexamethasone use to avoid the development of hydrocephalus in LMME, an experimental meningitis study in rabbits observed that administration of corticosteroids during the early stages of acute bacterial meningitis reduced CSF outflow resistance [22]. However, in our clinical series we could not demonstrate a useful effect of dexamethasone administered for 2 days in preventing hydrocephalus. In any case, the possibility that dexamethasone might have some protective effect for avoiding or modifying the development of hydrocephalus in a particular group of patients with LMME could not be totally ruled out.

Seizures occur frequently in C-ABM (15–24 %) [3, 24, 25], mainly in pneumococcal meningitis (28 %) [26], and are associated with increased mortality (41 %) [24]. For this reason, since 1987 antiseizure prophylaxis with phenytoin has been systematically administered at our centre when pneumococcal meningitis was suspected, with good results [27]. In the present series of LMME, 7/59 (12 %) elderly patients with underlying diseases and 2/7 (29 %) coma at admission who did not receive antiseizure prophylaxis suffered from seizures; other studies have reported similar results (7–17.1 %) [7, 8, 23]. In addition, a trend towards a higher neurological mortality was observed in this group. While antiseizure prophylaxis was not identified as a protective factor for mortality, no seizures were observed among the 13 patients receiving this adjuvant therapy. There is no information about use of anticonvulsants in patients with LMME, so in the absence of future studies, we think that they could be considered in elderly patients with a low level of consciousness at admission.

Listeria monocytogenes rhombencephalitis has rarely been analysed separately from meningitis and the clinical form of presentation has not been evaluated as a prognostic factor in previous case series [28, 29]. In our study, rhombencephalitis occurred in roughly 20 % of cases of LMME, as a more subacute form of the disease, associated with focal disease and causing more frequent sequelae. Interestingly, we observed fewer neurologic sequelae in patients receiving adjuvant therapy with dexamethasone.

Our study has several limitations. First, it is an observational study in which: (a) CT was not performed systematically at admission, three patients without CT at admission who presented early mortality could have presented it and so hydrocephalus may have been underdiagnosed; (b) The fact that prophylaxis with dexamethasone and phenytoin or antibiotic treatment were not administered randomized in all patients influenced the assessment of the real effect of these treatments; (c) The small sample size may have influenced on the fact that we mostly found trends and our relevant clinical findings were not strong statistically significant results. However, this is a large series of LMME homogeneously recorded at a single centre, including episodes diagnosed not only by CSF culture but also by positive blood culture for *L. monocytogenes* and CSF pleocytosis, and offers a more complete perspective of the disease than other reported series [8, 10, 30]. In addition, the detailed analysis focusing on factors involved in short-term mortality and sequelae provides information with the potential for influencing outcome in these patients.

Due to its frequency and high mortality and morbidity, LMME is a relevant current clinical problem. Meningitis and rhombencephalitis are two distinct clinical forms of the disease with different outcomes. Inappropriate empirical antibiotic therapy and the presence of hydrocephalus were the main prognostic factors for mortality. Meanwhile, rhombencephalitis and focal disease were the main prognostic factors for sequelae. The outcome may be improved by means of appropriate empirical antibiotic therapy, suspicion and careful management of hydrocephalus. Our data suggest that use of adjuvant dexamethasone or phenytoin in a subgroup of these patients might have a benefit, but we need more evidence to confirm this hypothesis.

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Conflict of interest The authors have no conflicts of interest and/or financial disclosures to declare.

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B. Prevention and treatment of infection of CSF devices used for hydrocephalus

B.1. Management of ventriculoperitoneal shunt infections in adults

Aim 1. To assess the efficacy of the treatment strategies in an adult cohort of VP shunt infections

Aim 2. To identify risk factors predicting failure in the treatment of VP shunt infection.

Article 2. *Management of Ventriculoperitoneal Shunt Infections in Adults: Analysis of Risk Factors Associated With Treatment Failure.* **Pelegrín I**, Lora-Tamayo J, Gómez-Junyent J, Sabé N, García-Somoza D, Gabarrós A, Ariza J, Viladrich PF, Cabellos C. Clin Infect Dis. 2017; 64: 989-997.

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MAJOR ARTICLE

Management of Ventriculoperitoneal Shunt Infections in Adults: Analysis of Risk Factors Associated With Treatment Failure

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Background. Little is known regarding the optimal treatment of ventriculoperitoneal (VP) shunt infections in adults. Our aim was to assess the efficacy of treatment strategies and to identify factors that predict failure.

Methods. Retrospective, observational study of patients aged ≥12 years with VP shunt infections (1980 -2014). Therapeutic approaches were classified under 4 headings: only antibiotics (OA), one-stage shunt replacement (OSSR), two-stage shunt replacement (TSSR), and shunt removal without replacement (SR). The primary endpoint was failure of the treatment strategy, defined as the absence of definite cerebrospinal fluid (CSF) sterilization or related mortality. The parameters that predicted failure were analyzed using logistic regression.

Results. Of 108 episodes (51% male, median age 50 years), 86 were analyzed. Intravenous antibiotics were administered for a median of 19 days. Eighty episodes were treated using strategies that combined antibiotic and surgical treatment (37 TSSR, 24 SR, 19 OSSR) and 6 with OA. Failure occurred in 30% of episodes, mostly due to lack of CSF sterilization in OSSR and OA groups. Twelve percent died of related causes and 10% presented superinfection of the CSF temporary drainage/externalized peritoneal catheter. TSSR was the most effective strategy when VP shunt replacement was attempted. The only independent risk factor that predicted failure was retention of the VP shunt, regardless of the strategy.

Conclusions. This is the largest series of VP shunt infections in adults reported to date. VP shunt removal, particularly TSSR when the patient is shunt dependent, remains the optimal choice of treatment and does not increase morbidity.

Keywords. ventriculoperitoneal shunt infection; CSF shunt; adult; treatment.

Ventriculoperitoneal (VP) shunts drain excess cerebrospinal fluid (CSF) from the cerebral ventricles, commonly to the peritoneal cavity. These devices have dramatically reduced the morbidity and mortality rates associated with hydrocephalus. However, shunt infection is a common complication, with a rate ranging from 5.6% to 12.9% [1].

Despite the major consequences of infection and the fact that physicians have more than 50 years of experience with this problem, no treatment guidelines are available [2, 3]. Since antibiotics alone offer limited efficacy in the management of VP shunt infection (VPSI) [4, 5], expert recommendations state that a combination of antibiotic and surgical treatment is required to achieve the best chance of definitive cure. These recommendations are based on case series, expert opinion, and a single prospective randomized study published decades ago [4]. In addition, only a few authors have evaluated shunt infections in adults and none of them included patients carrying a VP shunt exclusively [5–8].

The latest research has focused on the prevention of VPSI by implementing standardized protocols [9] or by using antimicrobial-impregnated/silver-processed CSF shunts [10]. However, no attempts have been made to identify risk factors for treatment failure in an episode of VPSI in adults. Moreover, the optimal route of administration and duration of antibiotics, the risk of potential superinfection of CSF temporary drainages or externalized peritoneal VP shunt catheters, and the best timing for shunt exchange have yet to be established.

The initial therapeutic approach is of paramount importance because treatment failure may make additional surgery and supplementary antibiotic courses necessary. This lengthens hospital stay and increases the risk of nosocomial infections.

In this retrospective analysis of a large cohort of adult patients with VPSI, we assessed the efficacy of our treatment strategies and identified factors that predict failure.

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METHODS

Setting and Patients

A retrospective, observational study was carried out at the Hospital Universitari de Bellvitge (Barcelona, Spain), a referral center for central nervous system infections and neurosurgery in adults; it has a catchment area of more than 1 million inhabitants. Between 1980 and 2014, all episodes of VPSI in patients aged ≥12 years were prospectively identified and recorded. Four independent infectious diseases consultants retrospectively reviewed the medical records of all episodes of CSF shunt infections, and 3 other experts later evaluated each episode according to predefined criteria. The following variables were included in a specifically designed Microsoft Access database: age, gender, underlying neurosurgical disease, reason for CSF shunting, type of CSF shunt, route of infection, clinical presentation, time to diagnosis, laboratory data, microbiological findings, antibiotic treatment received, surgical approach, need for an external ventricular drainage catheter (EVDC) or external lumbar drainage catheter (ELDC), and outcome.

None of the VP shunts were silver coated or impregnated with antibiotics. In accordance with our hospital protocol, a single prophylactic dose of cefuroxime was administered at the time of anesthesia induction.

CSF samples were obtained from an aseptic puncture of the CSF reservoir, through the externalized peritoneal catheter (PCath), or via lumbar puncture. Microorganisms were identified according to standard criteria [11] after samples had been seeded in thioglycolate broth and 5% sheep blood and chocolate agar and incubated for 10 days.

Definitions

An episode of infection was defined as the presence of clinical features compatible with a positive culture from CSF, VP shunt tip, or from exudate swabs obtained from wounds overlying the implant material. The time to infection was established as the number of days between the placement of the VP shunt or its last surgical revision and the onset of symptoms. Coma was defined when patients scored ≤8 in the Glasgow coma scale at admission. Hydrocephalus at admission was diagnosed following Evan's criteria and considered when ventricular size was larger than in a previous computed tomography scan. CSF sterilization time was established as the number of days between the initiation of therapy and first negative CSF culture.

Antibiotic and Surgical Management

In all patients with a suspected VPSI, blood cultures and a CSF sample were recovered. Distal externalization of the PCath was performed in cases of a strong suspicion of infection and/or malfunction. After these procedures, all patients followed our empirical treatment protocol, which has been in place since 1985: intravenous vancomycin 1 g twice daily ± ceftazidime or meropenem 2 g 3 times daily. Before 1985, several empirical combinations of antibiotics included cloxacillin or vancomycin ± aminoglycosides or antipseudomonal penicillins. Once antimicrobial susceptibility was available, antibiotics were adjusted accordingly.

The treatment strategies for all VPSI episodes were classified under the following 4 headings based on an intention-to-treat analysis: only antibiotics (OA) without VP shunt removal; VP shunt removal (SR) without shunt replacement; one-stage shunt replacement (OSSR), that is, the VP is removed and replaced by a new device in a 1-step exchange procedure, ideally after the CSF has been sterilized with antibiotics; and two-stage shunt replacement (TSSR), that is, a first surgical step to remove the VP shunt, a shunt-free time under antibiotic treatment in order to sterilize the CSF, and a second surgical procedure to reimplant a new device. The need for EVDC/ELDC depends on the type of underlying neurological disorder. The 4 types of strategies include intravenous ± intraventricular antibiotics.

The decision to initiate surgical and antimicrobial therapy was made by the neurosurgeon and the infectious diseases consultant. When the first chosen strategy failed, a salvage therapy was provided, if feasible.

Outcome and Follow-up

Follow-up was recorded by review of hospital admissions and outpatient clinic visits. The primary endpoint was failure of the first treatment strategy and was defined as the lack of definite CSF sterilization within 14 days or related mortality. Cure was defined as cessation of initial symptoms and signs of infection and a negative CSF culture after treatment, if available.

Mortality was recorded during hospital stay and was classified as related to the VPSI if death occurred during treatment and was due directly to a persistent infection or its complications.

Statistical Analyses

Comparative analyses were performed with the χ^2 test or the Fisher exact test for categorical variables, as appropriate, and the Kruskal-Wallis test or the Mann-Whitney *U* test for continuous variables.

Independent predictors of treatment failure were identified via univariate analysis and multivariate logistic regression. We also performed a subanalysis of shunt-dependent patients who required surgery (namely, those undergoing OSSR and TSSR).

All analyses were 2-tailed and a P value < .05 was considered statistically significant. Data were analyzed using SPSS software, version 18.0.

RESULTS

Description of the Series

One hundred and eight episodes of VPSI in 101 patients were included. Fifty-five episodes (51%) occurred in males, and

median age was 50 years (interquartile range [IQR], 31–70). Baseline features and clinical presentation are shown in Table 1. Ninety-four (87%) episodes were monomicrobial. The most frequent microorganisms causing infection were staphylococci (63 episodes [58%]) and Gram-negative Bacilli (GNB) (15 episodes [14%]). Detailed microbiological etiology of episodes is shown in Table 2. Infection presented a median of 31 days (IQR, 11–254) after surgery, and most episodes were diagnosed within 6 months (72%). The relations between the route of infection, time to infection, and microbiology are shown in Supplementary Table 1.

Table 1. Epidemiological and Clinical Characteristics at Admission and Laboratory Findings of 108 Episodes of Ventriculoperitoneal Shunt Infections in Adults

Age, y (median, IQR)	50 (31–70)
Gender (male)	55/108 (51%)
Underlying neurological condition	
Brain tumor	25/108 (23%)
Subarachnoid hemorrhage	19/108 (18%)
Normal pressure hydrocephalus	17/108 (16%)
Stenosis of the cerebral aqueduct	11/108 (10%)
Arachnoid cyst	6/108 (6%)
Intracerebral hemorrhage	5/108 (5%)
Arteriovenous malformation	3/108 (3%)
Other	17/108 (16%)
Unknown	5/108 (5%)
Reason for shunt placement	
Communicating hydrocephalus	59/108 (55%)
Obstructive hydrocephalus	42/108 (39%)
Other	7/108 (6%)
Clinical characteristics	
Temperature >38°C	85/107 (79%)
Altered mental state	63/106 (59%)
Coma	6/106 (6%)
Headache	34/103 (33%)
Local inflammatory signs	43/93 (46%)
Abdominal pain	44/107 (41%)
Neck stiffness	38/106 (36%)
Vomit	34/106 (32%)
Seizures	7/106 (7%)
Hydrocephalus[a]	33/88 (38%)
Laboratory findings	
Positive blood cultures	6/107 (6%)
Positive CSF Gram stain	31/107 (29%)
Positive CSF culture	92/107 (86%)
CSF from shunt valve	63/92 (68%)
Ventricular CSF	18/92 (20%)
Lumbar CSF	7/92 (8%)
Positive shunt tip culture	45/91 (49%)
Positive wound swab culture	21/92 (23%)
WBC count, 10^9/L (median, IQR), n = 67	10.5 (8.2–13.7)
CSF WBC count, cells/μL (median, IQR), n = 92	36 (2–194)
CSF protein level, g/L (median, IQR), n = 93	0.53 (0.23–1.07)
CSF glucose level, mmol/L (median, IQR), n = 77	3.4 (2.8–3.8)
Hypoglycorrhachia (<40 mg⁄dL)	15/67 (22%)

Data are proportions of patients, unless otherwise indicated.

Abbreviations: CSF, cerebrospinal fluid; IQR, interquartile range; WBC, white blood cell.

[a]Hydrocephalus at admission was diagnosed following Evan's criteria and considered when ventricular size was increased.

Treatment Approach

Among the 108 episodes of VPSI, complete data for analysis of treatment approach were available for 86 episodes (80%) in 80 patients.

Intravenous antibiotics were administered in all episodes for a median time of 19 days (IQR, 13–24), while intraventricular antibiotics were administered in 5/86 episodes (6%) for a median time of 10 days (IQR, 4–23). Tailored antibiotic therapy is summarized in Table 2.

Details of the surgical approach are summarized in Table 3. The choice of surgical strategies has not significantly changed over time, except for the OA strategy, which was abandoned progressively (from 25% in the 1980s to 0% starting in 2000, $P < .003$) (see Supplementary Figure 1). The VP shunt could be removed without further replacement in 24 episodes (28%) a median time of 6 days (IQR 3–9) after diagnosis. None of these patients required further management of their intracranial pressure through CSF drainage.

Shunt exchange was attempted in 56 episodes (65%), TSSR being the most frequent surgical choice (37 episodes [43%]). In TSSR, the first stage was performed within a median of 4 days (IQR, 1–8) of diagnosis. Eighteen patients (49%) required the placement of an EVDC/ELDC. The second stage was feasible in 34/37 episodes (92%) after a median time of 17 days (IQR, 11–27). In 3 episodes (8%) shunt replacement could not be performed due to early mortality. OSSR was attempted in 19 episodes (22%), in 17 of which the PCath was previously externalized (90%). The replacement was completed in 10/19 cases (53%) after a median time of 18 days (IQR, 11–29).

Outcome

Sixty of 86 (70%) episodes were cured after a median follow-up of 36 weeks (IQR, 10–198). Failure was observed in 26/86 (30%) episodes; in 16 (19%) there was lack of CSF sterilization, 7 (8%) episodes presented related death with infection, and 3 (4%) presented both. The 16 patients with lack of CSF sterilization underwent salvage therapy, and in all but 1, CSF sterilization was finally achieved (Supplementary Figure 2).

The univariate analysis showed that episodes with an unfavorable outcome presented more frequently with coma at admission (15% vs 0%), higher CSF white blood cell count (90 [IQR, 16–313] vs 24 [1–81]), and were more likely to be treated with shunt retention (50% vs 2%; see Table 4). In the multivariate analysis, the only independent risk factor for treatment failure was management that included VP shunt retention (odds ratio [OR], 46.040; 95% confidence interval [CI], 5.301–399.875; $P < .001$).

Table 2. Etiology of 108 Episodes of Ventriculoperitoneal Shunt Infection and Treatment Strategies and Outcome in 86 Episodes According to Etiology

Monomicrobial Episodes (n = 94)				n = 86 Episodes With Strategy Analysis				
	Genus	Species	n (%)		Intravenous Antibiotic	Intraventricular Therapy[a]	Strategy[b]	Failure
Gram-positive bacteria, 79 (73%)	Staphylococci, 63 (58%)	Coagulase-negative staphylococci[c]	47 (44)	N = 37[d]	22 Vancomycin 4 Cloxacillin 4 Cotrimoxazole 2 Teicoplanin 2 Penicillin/Ampicillin 1 Third generation cephalosporin 1 Quinolones 1 Linezolid 5 Rifampin[e]	4 Vancomycin	7 TSSR 10 OSSR 9 SR 4 OA	14/40 (35%)
		Staphylococcus aureus[f]	16 (15)	N = 14	5 Vancomycin 5 Cloxacillin 1 Cotrimoxazole 1 Quinolones 1 Vancomycin + cotrimoxazole 2 Rifampin	-	7 SR 5 TSSR 2 OSSR	3/14 (21%)
	Enterococci, 5 (5%)	*Enterococcus faecalis*	4 (4)	N = 1[d]	Ampicillin + gentamicin	-	2 TSSR	0/2 (0%)
		Enterococcus faecium	1 (1)					
	Streptococci, 3 (3%)	*Streptococcus mitis*	1 (1)	N = 1	Penicillin/Ampicillin	-	1 OA	0/1 (0%)
		Streptococcus pneumoniae	1 (1)					
		Streptococcus pyogenes	1 (1)					
	Gram-positive bacilli or coccibacilli, 8 (7%)	*Propionibacterium acnes*	6 (6)	N = 6	3 Vancomycin 2 Penicillin/Ampicillin 1 Third generation cephalosporin	-	2 OSSR 3 SR 1 OA	2/6 (33%)
		Bacillus spp.	1 (1)					
		Rhodococcus non equi	1 (1)					
Gram-negative bacteria, 15 (14%)	Pseudomonas, 4 (4%)	*Pseudomonas aeruginosa*	3 (3)		6 Third generation cephalosporin 4 Meropenem	1 Colistin sulfomethate sodium	5 OSSR 5 TSSR	
		Pseudomonas alcaligenes	1 (1)		1 Meropenem + ciprofloxacin 1 Ceftriaxone + metronidazole		2 SR	
	Acinetobacter, 1 (1%)	*Acinetobacter calcoaceticus*	1 (1)	N = 12				6/12 (50%)
	Enterobacteriaceae, 10 (9%)	*Klebsiella pneumoniae*	4 (4)					
		Klebsiella oxytoca	1 (1)					
		Serratia marcescens	1 (1)					
		Escherichia coli	2 (2)					
		Enterobacter aerogenes	1 (1)					
		Salmonella typhi	1(1)					
Polymicrobial episodes[g] (n = 14)				N = 11	Several antibiotics	-	8 TSSR 3 SR	1/11 (9%)

Abbreviations: OA, only antibiotics; OSSR, one-step shunt replacement; SR, shunt removal without replacement; TSSR, two-step shunt replacement.

[a]The route of administration was an externalized distal catheter in 3 episodes, an Ommaya reservoir in 1 episode, and via an external ventricular drainage catheter in 1 episode. Vancomycin 10–20 mg once daily was administered in 4 episodes caused by coagulase-negative staphylococci, and colistin sulfomethate sodium 5 mg every 12 hours was administered in 1 episode caused by *A. calcoaceticus*.

[b]The strategies were as follows: OA, only antibiotics; OSSR, one-step shunt replacement; SR, shunt removal without replacement; TSSR, two-step shunt replacement.

[c]Coagulase-negative staphylococci: 22 (20%) were identified as *S. epidermidis*, 2 (2%) as *S. haemolyticus*, and 1(1%) as *S. intermedius*. In 22 (20%) of the isolates, staphylococci species were not identified.

[d]Antibiotic treatment information was unavailable for 3 cases of staphylococcal infection and 1 case of enterococci infection.

[e]Rifampin was always used in combination with other agents.

[f]Seven episodes out of 16 were methicillin-resistant *Staphylococcus aureus*.

[g]Polymicrobial: combinations of several Gram-negative bacilli and Gram-positive bacteria in 7/14 (*Pseudomonas*, Enterobacteriaceae, or occasionally Gram-negative anaerobic bacilli with staphylococci (including methicillin-resistant *S. aureus* or *Propionibacterium acnes*)], Gram-positive bacteria in 6/14 episodes (primarily *P. acnes* and coagulase-negative staphylococci), and Gram-negative bacilli in 1/14.

A nonsignificant progressive downfall in the percentage of failure was observed over time (from 38% in the 1980s to 27% in the last decade; $P = .572$; see Supplementary Figure 1). The etiology of infection was not associated with failure, although episodes caused by GNB presented higher failure rates (23% vs 10%; $P = .181$). The effect of antibiotics on prognosis was

difficult to analyze, as etiologies and regimes were heterogeneous. Still, among episodes of staphylococcal infection, the use of rifampin was associated with a nonsignificant better prognosis; only 1 failure (14%) was observed in the 7 patients treated with rifampin vs 16/44 (36%) who did not receive it ($P = .421$). Interestingly, the only episode that failed and included rifampin was treated with OA.

Regardless of the surgical strategy chosen, removal of the VP shunt was associated with a better outcome (Tables 3 and 4). Episodes treated with TSSR or SR had a higher cure rate (89% and 83%, respectively) than those treated with the other 2 strategies ($P < .001$). There were no statistical differences in mortality between strategies ($P = .408$).

Superinfection of the EVDC/ELDC or externalized PCath was present in 9/86 (10%) episodes and did not lead to any changes in the first strategy chosen. Complications related to the placement of an EVDC/ELDC were present in 7/22 (32%): infection of the ELDC (3) or EVDC (1), EVDC blockages requiring at least 1 change (2), and intraparenchymal hemorrhage secondary to its placement (1). None of the infections caused mortality. Superinfection of the externalized PCath occurred in 5 episodes after a median of 18 days of externalization (IQR, 12–53).

Related mortality was recorded in 10 episodes. The median time from diagnosis to death was 34 days (IQR, 13–43 days). Three patients (30%) died due to persistent infection with severe ventriculitis. The other 7 (70%) had a sterile CSF at time of death but presented several complications related to infection: 3, neurologic impairment; 2, respiratory failure; 1, gastrointestinal bleeding; and 1 candidemia.

TSSR vs OSSR

Episodes failed more frequently with OSSR than TSSR (13/19 [68%] vs 4/37 [11%]; OR, 17.875; 95% CI, 4.327–73.850; $P < .001$). Consequently, hospital stay was longer in OSSR than in TSSR (58 days vs 40 days; $P = .009$). A nonsignificant trend toward higher related mortality and longer intravenous treatment was observed among patients managed with OSSR (21% vs 8%; $P = .212$ and 24 days vs 19 days; $P = .312$, respectively; see Table 3).

Only 10/19 (53%) patients managed with OSSR appeared to achieve CSF sterilization and, for this reason, underwent 1-step shunt exchange, as planned. However, of these 10, 4 experienced failure after the replacement, primarily due to persistence of the same infection, and only in 1 episode due to a related death. The replacement was performed at a median time of 21 days (IQR, 18–22) in the 6 episodes that were cured, and at a median time of 11 days (IQR, 3–17; $P = .032$) in the 4 episodes that finally failed.

Table 3. Comparison of Management and Outcome Regarding the Strategy Used in 86 Episodes of Ventriculoperitoneal Shunt Infection

		Total (86)	Only Antibiotics (n = 6)	One-Step Shunt Replacement (19)	Two-Step Shunt Replacement (37)	Shunt Removal Without Replacement (24)	*P* Value[a]	*P* Value[b]
Management	Hospital stay, days (median, IQR)	41 (25–71)	67 (29–94)	58 (35–91)	40 (25–66)	28 (18–49)	.047	.009
	Days of intravenous ATB, median, IQR	19 (13–24)	20 (16–24)	24 (13–27)	19 (15–23)	18 (12–20)	.247	.312
	Intrathecal treatment	5 (9%)	0 (0%)	2 (11%)	1 (3%)	2 (8%)	. 553	.263
	Externalization	48 (56%)	1 (17%)	17 (90%)	21 (58%)	9 (38%)	.002	.016
	External ventricular drainage catheter–external lumbar drainage catheter	22 (26%)	0 (0%)	1 (5%)	18 (49%)	3 (13%)		
Outcome	CSF sterilization	67 (79%)	1 (17%)	9 (47%)	35 (95%)	22 (92%)	<.001	<.001
	Time to CSF sterilization in days, n/ median	n = 60/7	N = 0	N = 9/ 9	N = 32/ 9	N = 20/ 4	.139	.423
	Superinfection of external ventricular drainage catheter/ shunt	9 (10%)	0 (0%)	4 (21%)	3 (8%)	2(8%)	.403	.219
	Failure	26 (30%)	5 (83%)	13 (69%)	4 (11%)	4 (17%)	<.001	<.001
	Related mortality	10 (12%)	0 (0%)	4 (21%)	3 (8%)	3 (13%)	.408	.212
	Overall mortality	14 (16%)	0 (0%)	5(26%)	4 (11%)	3(13%)	.291	.247

Data are number (%) of episodes unless time measures are indicated. Percentages were rounded.

Abbreviations: ATB, antibiotics; CSF, cerebrospinal fluid; IQR, interquartile range.

[a]Comparison between all strategies using χ^2 or Kruskal-Wallis tests.

[b]Comparison between 1-step shunt replacement (OSSR) and 2-step shunt replacement using χ^2 or Mann-Whitney *U* tests. OSSR was associated with failure (unadjusted odds ratio, 17.875; 95% confidence interval, 4.327–73.850; $P < .001$).

Table 4. Univariate and Multivariate Analysis of Risk Factors for Failure in 86 Episodes of Ventriculoperitoneal Shunt Infections in Adults

	Cure, n = 60	Failure, n = 26	*P* Value	Adjusted Odds Ratio	*P* Value
Age, y (median, IQR)	52 (37–70)	63 (28–74)	.735	-	-
Gender (male)	32 (53%)	13 (50%)	.776	-	-
Underlying neurological condition					
Brain tumor	16 (27%)	4 (15%)	.165		
Subarachnoid hemorrhage	12 (20%)	4 (15%)			
Normal pressure hydrocephalus	12 (20%)	4 (15%)			
Stenosis of the cerebral aqueduct	7 (12%)	2 (8%)			
Arachnoid cyst	2 (3%)	3 (12%)			
Intracerebral hemorrhage	0 (0%)	3 (12%)			
Arteriovenous malformation	1 (2%)	1 (4%)			
Reason for shunt placement					
Communicating hydrocephalus	34 (57%)	13 (50%)	.562		
Obstructive hydrocephalus	21 (35%)	12 (46%)			
Time to infection, days (median, IQR)	30 (11–172)	19 (6–390)	.489		
Clinical characteristics					
Temperature >38°C	48 (80%)	22 (85%)	.767		
Altered mental state	32 (53%)	18 (69%)	.170		
Coma	0 (0%)	4 (15%)	.007		
Headache	20 (33%)	4 (15%)	.182		
Local inflammatory signs	29 (47%)	11 (40%)	.560		
Abdominal pain	25 (42%)	9 (35%)	.539		
Neck stiffness	19 (29%)	9 (36%)	.789		
Vomit	17 (28%)	8 (31%)	.819		
Seizures	3 (5%)	1 (4%)	1		
Hydrocephalus[a]	17 (28%)	7 (27%)	1		
Laboratory findings					
Positive CSF Gram stain	17 (28%)	7 (27%)	1		
Positive CSF culture	50 (83%)	23 (88%)	.715		
CSF white blood cell count, cells/μL (median, IQR), n = 76	24 (1–81)	90 (16–313)	.027	1.001 (1.000–1.002)	.076
CSF protein level, g/L (median, IQR), n = 76	0.53 (0.25–0.88)	0.45 (0.21–1.04)	.865		
CSF glucose level, mmol/L (median, IQR), n = 71	3.7 (3–3.9)	3.3 (2.2–3.8)	.196		
Hypoglycorrhachia (<40 mg⁄dL)	7/39 (18%)	3/14 (21%)	1		
Positive blood cultures	2 (3%)	2 (8%)	.594		
Leukocyte count, $\times 10^9$/L (median, IQR), n = 63	10.3 (7.3–13.7)	10.2 (8.4–12.8)	.951		
Monomicrobial episodes (n = 75)					
Staphylococcus aureus	11 (18%)	3 (12%)	.361		
Coagulase-negative staphylococci	26 (43%)	14 (54%)	.743		
Propionibacterium acnes	3 (5%)	2 (8%)	1		
Gram-negative bacilli	6 (10%)	6 (23%)	.181	-	-
Polymicrobial episodes (n = 11)	10 (17%)	1 (4%)	.161		
Management					
External ventricular drainage catheter	19 (32%)	3 (12%)	.062		
Externalization	31 (52%)	17 (65%)	.166		
Intrathecal treatment	3 (5%)	2 (8%)	.627		
Complications of external ventricular drainage catheter/ external lumbar drainage catheter	7 (12%)	0 (0%)	.273		
Ventriculoperitoneal shunt retention	1 (2%)	13 (50%)	<.001	46.04 (5.301–399.9)	<.001

According to a preanalytical plan, the initial multivariate analysis included the variables sex, age, infection caused by gram-negative bacilli, as well as those parameters with a *P* value <.05 in the univariate analysis, that is, ventriculoperitoneal shunt retention and CSF white blood cell count. The parameter "coma" was not included in the model because of statistical problems due to its inherent inability to predict failure. All of these variables were submitted to a backward stepwise selection process. Variables included in the initial model but excluded during this process are identified by a hyphen (-).

Abbreviations: CSF, cerebrospinal fluid; IQR, interquartile range.

[a]Hydrocephalus at admission was diagnosed following Evan's criteria and considered when ventricular size was increased.

Table 5. Treatment and Outcome of Cerebrospinal Fluid Shunt Infection Adult Case Series Reported in the Literature

	Princi et al [5]	Spanu et al [6]	Sacar et al [13]	Brown et al [18]	Conen et al [7]	von der Breile et al [8]	Our Series
Year of publication	1979	1986	2006	2006	2008	2012	2016
Number of total/adult episodes	9/9	23/23	22/12	40/16	78/78	92/71	108/108
Period of the study	-	-	2000–2004	1986–2003	1996–2006	2002–2008	1980–2014
Type of CSF shunt	5 Holter	10 EVDC	-	42 VP	65 VP	87 VP	VP
	2 Accu-Flo	7 VA		1 VA	7 VA	5 VA	
	2 External	5 VP			5 LP		
		1 other			1 central nervous system reservoir		
Intravenous antibiotics	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Intrathecal antibiotics	No	No	No	Yes	No	No	5/86 (9%)
Days of intravenous antibiotics, median, R or IQR	-	7 days	-	14 (R 7–21)	18 (R 4–91)	14 (R 4–80)	19 (IQR 13–24)
First line strategy							
OA	9/9	-	-	43/43	15/78	-	6/86
OSSR	-	-	-	-	8/78	-	19/86
TSSR	-	23/23	22/22	-	18/78	75/92	37/86
			EVDC (22)		EVDC (12)	EVDC (75)	EVDC/ELDC (18)
SR	-	-	-	-	37/78	8/92	24/86
CSF shunt removal	0/9 (0%)	23/23 (100%)	22/22 (100%)	0/43 (0%)	63/78 (81%)	83/92 (90%)	72/86 (84%)
Time until removal (days)	-	-	-	-	-	-	6 (IQR 2–12)
Time until replacement (days)	-	-	-	-	≤ 30 d	Median 18 (R 7–131)	Median 17 (IQR 11–27) TSSR
							Median 18 (IQR 11–21) OSSR
CSF sterilization	6/9 (67%)	20/23 (87%)	-	28/30 (93%) coagulase-negative Staphylococci	75/78 (96%)	Recurrence 13%	67/86 (79%)
				3/7 (43%) *S. aureus*			
Related mortality	3/9 (33%)	-	3/22 (14%)	3/39 (8%)	7/74 (11%)	1/78 (1%)	10/86 (12%)
Hospital stay, days (median, R or IQR)	-	-	-	Median 16 (R 4–60)	Median 26 (R 1–100)	Median 29 (R 11–194)	Median 41 (IQR 25–71)
Follow-up, y (median, R or IQR)	-	-	-	Median, R 0.5–10.6	4.6 (R 0.1–11.1)	3.75 (R 0.4–7.2)	0.7 (0.2–3.8)
Risk factors for failure	-	-	-	-	-	-	Retain the shunt

Abbreviations: CSF, cerebrospinal fluid; ELDC, external lumbar drainage; EVDC, external ventricular drainage catheter; IQR, interquartile range; LP, lumboperitoneal; OA, only antibiotics; OSSR, one-step shunt replacement; R, range; SR, shunt removal without replacement; TSSR, two-step shunt replacement; VA, ventriculoatrial; VP, ventriculoperitoneal.

DISCUSSION

Our series is the largest cohort of VPSI in adults published to date and the first study designed to evaluate the treatment outcome in VPSI focusing on CSF sterilization, mortality, and superinfection. As such, it offers a more complete perspective of management than previous reports. We also performed the first statistical analysis to evaluate risk factors and concluded that management, including VP shunt retention, was the only statistically significant predictor of failure.

Ninety-three percent of episodes were treated using a strategy that combined antibiotic and surgical treatment. Removal of the infected device is standard practice in foreign body–associated infections, since the odds of curing the infection are increased [12]. Therefore, when a VPSI is diagnosed, the treatment strategy must be decided upon immediately, and the need for the VP shunt must be reconsidered. Among patients who are not CSF shunt dependent, SR is the preferred strategy. The clinical challenge lies in the treatment of patients who do need the CSF shunt, which is why we focused on them in this study.

TSSR was the most successful strategy, with a cure rate of 89%, similar to the rates reported in previous studies (86%–100%; see Table 5) [6–8, 13]. In addition, TSSR presented low mortality (8%) and the highest CSF sterilization rate (95%). Many patients undergoing TSSR may need an EVDC/ELDC (50% in our cohort). Little information is available about complications related with EVDC/ELDC placement, but it may lead to a worse outcome.

In our study, complications, including superinfection of the ELDC/EVDC, did not require any important diversion from the treatment plan and did not lead to a fatal outcome. The ideal time between removal of the infected VP shunt and placement of a new one in order to guarantee cure has not been established. In our experience, the second-step surgery was performed after a median of 17 days, a period that is in the lower range of previous reports (18–30 days) [7, 8]. However, in 25% of our episodes managed with TSSR, the VP shunt was replaced within 12 days with no relapse. In those episodes, a CSF culture sample was taken through a different drainage catheter during the first surgical procedure, with antibiotic treatment until the results were available. If negative, the new VP shunt was placed safely in a shorter time.

In contrast to the results of TSSR, the outcome of our patients managed with OSSR was poor; the cure rate was 33%, which is much lower than the 88% reported in a similar series of adult CSF shunt infection [7]. These differences may be partially due to methodological and inclusion criteria. For example, half of our episodes could not actually have their VP shunt exchanged due to lack of CSF sterilization or blockages while the PCath was being externalized. This is a situation that reflects the real likelihood of failure when CSF sterilization with intravenous antibiotics is attempted. In addition, the number of GNB infections, supposedly associated with a worse outcome [14], was higher in our series. However, in the OSSR group in whom the VP shunt replacement was finally performed, the cure rate was 60%, similar to the rates reported in other pediatric cohorts [15–17]. In any case, it is important to note that some patients who appeared to have CSF sterilization at the time of VP shunt replacement relapsed after surgery. In fact, in patients in whom OSSR failed, the replacement was performed a median of 11 days earlier than in whom it succeeded. On the other hand, superinfection of the externalized PCath occurred in 21% of OSSR patients within a median time of 18 days. In our opinion, if OSSR is chosen, absolute CSF sterilization must be confirmed before replacement and the time of PCath externalization while the patient receives antibiotics must be weighed against the critical risk of superinfection. Episodes treated with OSSR presented significantly longer hospital stays than those treated with TSSR, leading to higher overall costs.

We cannot be certain that OSSR and OA would not have led to a higher and faster CSF sterilization rate if antimicrobial therapy had been optimized using systemic antibiotics with a more bactericidal profile, such as daptomycin or rifampin and/or intraventricular antibiotics. Addition of rifampin to the staphylococcal VPSI treatment without shunt removal seemed to be effective in selected patients [7, 18]. Although only a small number of our patients received rifampin, our data also suggest a better outcome for patients treated with a rifampin-based combination. While the role of intraventricular antibiotics remains controversial [19, 20], one report has claimed success in selected patients with coagulase-negative staphylococci shunt infections with a functioning system using intraventricular vancomycin plus systemic rifampin without shunt removal [18]. Unfortunately, in our limited experience, we did not identify any differences in prognosis.

The treatment of a VPSI with OA alone is discouraged by the low cure rate observed in our patients (17%) and in previous cohorts [4, 5, 15, 16], although further research using new antibiotics is required [21–23]. However, a notable exception to the rule of VP shunt removal is community-acquired bacterial meningitis, in which patients should be treated in the same way as those without VP shunts and which has a good prognosis.

Our study has several limitations. First, the decision to choose a first-line strategy or to start salvage therapy did not follow a defined protocol, a circumstance that may have biased our treatment groups and consequently our results. Specifically, there may be a selection bias, as the patients who did not undergo VP shunt removal may have presented underlying diseases and would therefore have been poor surgical candidates. Second, the nonsystematic use of intraventricular antibiotics and rifampin may have worsened our failure rate. Last, the sample size in some of the treatment groups was small, and we might not find strong statistically significant results.

In summary, VP shunt removal, particularly TSSR when the patient is shunt-dependent, remains the optimal choice of treatment of VPSI in adults and does not increase morbidity. OSSR and OA had a high failure rate but, if chosen, require careful management and an optimized antimicrobial schedule.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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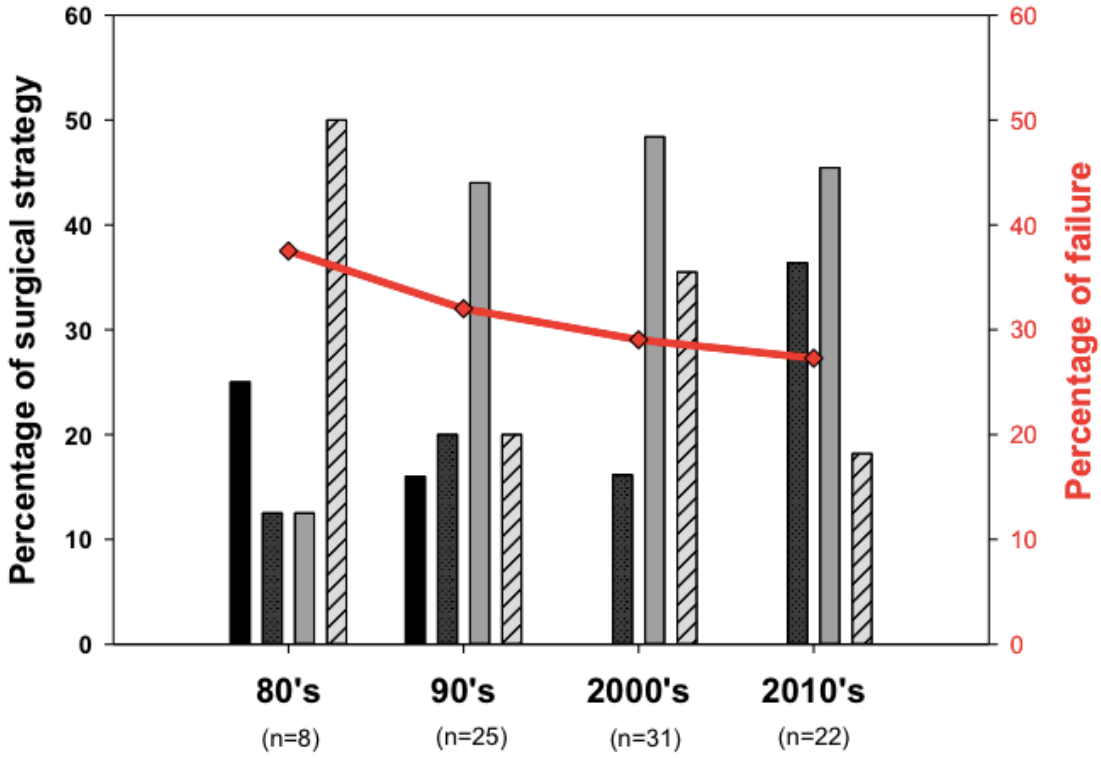
Supplementary Table 1. Relation between route of infection, time to infection and microbiology of 108 episodes of ventriculoperitoneal shunt infection

Etiology	N (%)	Route of Infection			Time to Infection		
		Local acquisition	Perforated gut	Hematogenous	<1month	1-6 months	>6 months
S. aureus	16 (15%)	16 (100%)	0 (0%)	0 (0%)	11 (69%)	3 (19%)	2 (13%)
CoNS	47 (44%)	47 (100%)	0 (0%)	0(0%)	21 (45%)	13 (28%)	13 (28%)
P. acnes	6 (6%)	6 (100%)	0 (0%)	0 (0%)	2 (33%)	1 (17%)	3 (50%)
GNB	15 (14%)	10 (67%)	5 (33%)	0 (0%)	11 (73%)	2 (13%)	2 (13%)
Enterococcus	5 (5%)	2 (40%)	3 (60%)	0 (0%)	3 (60%)	1 (20%)	1 (20%)
Streptococcus	3 (3%)	2 (67%)	0 (0%)	1 (33%)	1 (33%)	1 (33%)	1 (33%)
Rhodococus	1 (1%)	1 (100%)	0 (0%)	0(0%)	0 (0%)	0(0%)	1 (100%)
Bacillus	1 (1%)	1 (100%)	0 (0%)	0 (0%)	0(0%)	1 (100%)	0 (0%)
Polymicrobial	14 (13%)	10 (71%)	3 (21%)	1 (7%)	5 (36%)	2 (14%)	7 (50%)
Total	108 (100%)	95 (88%)	11 (10%)	2 (2%)	54 (50%)	24 (22%)	30 (28%)

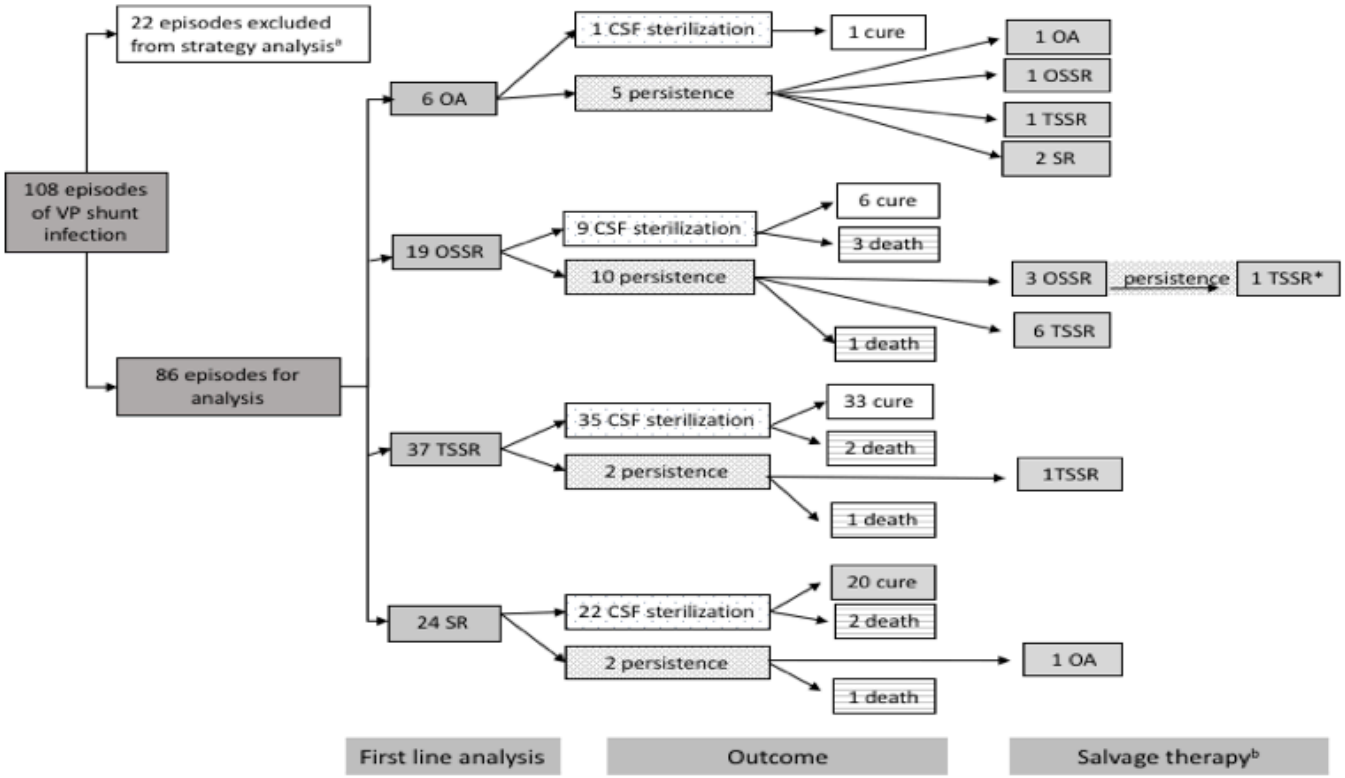
Abbreviations: CoNS: Coagulase Negative Staphylococci; GNB: Gram Negative Bacilli.

Supplementary Figure 1 – Trends of medical and surgical management of CSF-shunt infections and percentage of failure over time



Black solid bars: only antibiotics; dark dotted grey bars: one-stage shunt replacement; light solid grey bars: two-stage shunt replacement; light striped grey bars: shunt removal. The choice for only antibiotics was abandoned progressively (from 25% in the 80s to 0%) (Mantel-Haenszel test for linear trends, p=0.003). No significant variations over time were observed for the other strategies. A non-significant downfall in the percentage of failure (red line) was observed over time (from 38% to 27%, Mantel-Haenszel test for linear trends, p=0.572).

Supplementary Figure 2. First line treatment strategies, salvage therapy and outcome of VP shunt infections.



Abbreviations: 1. VP: ventriculoperitoneal. 2. CSF Cerebrospinal fluid. 3. OA: Only Antibiotics. 4. OSSR: One-Stage Shunt Replacement. 5. TSSR: Two-Stage Shunt Replacement 6. Shunt Removal without replacement.

a. Twenty-two episodes were excluded due to lack of sufficiently detailed data to analyse outcome of the strategy chosen

b. Outcome after salvage therapy was cure, except for one episode* who died after 3 line strategies.

B2. Prevention of External Ventricular Drain associated infections

Aim 1. To assess the *in vitro* antibacterial activity of a new impregnated external ventricular drainage catheter against MDR *A. baumannii.*

Article 3. *In vitro efficacy of a triclosan-impregnated external ventricular drainage catheter to prevent multi-drug-resistant Acinetobacter baumannii ventriculitis.* **Pelegrín I**, Ashraf W, Bayston R. Sent for publication.

In-vitro efficacy of a triclosan-impregnated external ventricular drainage catheter to prevent multi-drug-resistant *Acinetobacter baumannii* ventriculitis

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Running title: triclosan-impregnated external ventricular drainage catheter

Synopsis

Objectives: To investigate the *in-vitro* antibacterial activity of an impregnated external ventricular drainage catheter against three strains of multi-drug-resistant (MDR) *A. baumannii.*

Methods: Silicone EVD catheters were impregnated with three antimicrobials (rifampicin, trimethoprim and triclosan) and tested against three clinical isolates of MDR *A. baumannii*. Four assays were performed: (a) Biofilm formation; (b) Measurement of bacterial adhesion to plain silicone; (c) testing the ability of the catheter to kill 100% of the attached bacteria (tK100); and (d) in vitro challenge to determine the ability to prevent colonization under flow conditions (IVC). The surface of the lumens of all the tubing was analysed using scanning electron microscope.

Results: Differences were found in terms of biofilm formation and adherence to silicone between the three strains of MDR *A.baumannii,*. In the tK100 assay, all attached bacteria were killed at approximately 48hr. In the IVC model, after repeated high microbial loads challenges, 6/9 catheters remained free of colonization for at least three weeks. The other 3 become colonised at Day 24, 29 and 41, the first one being due to the most virulent strain.

Conclusions: The antimicrobial catheters were able to eradicate all bacteria that had become attached to the catheters, even under flow conditions. The new antimicrobial catheter promises to reduce MDR *A. baumannii* EVD infections over the first 3 weeks of use. Clonal outbreak strains with different virulence factors such as biofilm formation and silicone adherence might influence outcome in MDR *A. baumannii* ventriculitis.

1. Introduction

External ventricular drains (EVD) are used for diagnosis and treatment of raised intracranial pressure, after head trauma, intracranial haemorrhage or tumours, and they may be in place for a few days or up to 2–3 weeks. As the system is not totally internalized, and as CSF is often drawn from it for analysis and pressure monitoring, the risk of infection is high, with rates of up to 20%.[1,2] Ventriculitis increases the morbidity and mortality of these patients and their hospital stay, this leading to a higher overall consumption of economic and personal costs. [3-5]

In recent years, use of "bundles" of measures have been trialled to prevent EVD-associated infections, with a protocol violation as a significant risk factor for failure.[6,7] Furthermore, antibiotic-impregnated EVD catheters have recently been introduced in an attempt to reduce the risk of ventriculitis, with a report of a significant decrease of infection rates.[8-11] These antibiotic-impregnated EVD catheters containing rifampicin and clindamycin target Gram positive bacteria, mainly coagulase negative staphylococci, which are the most common cause.[2] However, nowadays the epidemiology of EVD-associated ventriculitis has changed and Gram negative bacteria have emerged as a considerable problem, especially in intensive care units, where multi-resistant strains causing infection are increasing.[12] In this setting, we have developed a new antimicrobial - impregnated EVD with potential activity against Gram positive and Gram negative bacteria except *Pseudomonas aeruginosa*.

Acinetobacter baumannii has been increasingly reported to cause nosocomial ventriculitis,[13,14] with a mortality rate up to 73%.[15] Due to its ability to cause outbreaks and to become resistant to antibiotics WHO has registered it as a nosocomial pathogen in which resistance is of great public health concern.[16] Moreover, treatment options are limited for multidrug resistant (MDR) *A. baumannii* central nervous system infections.[17]

Due to the importance of outbreaks of nosocomial ventriculitis caused by MDR *A. baumannii* and its difficult treatment we have assessed the efficacy of this new EVD catheter against strains of MDR *A. baumannii* in vitro.

2. Materials and Methods

2.1. Biomaterials

Medical grade silicone tubing, barium filled, internal diameter 1.5mm, external diameter 3mm, [Dow Corning Europe, Seneffe, Belgium] was used as controls.

2.2. Impregnation process

Lengths of silicone tubing, 35cm, were impregnated using a previously published method.[18] Briefly, the chosen antimicrobials (rifampicin R3501, trimethoprim base T7883, and triclosan (Irgasan), all from Sigma-Aldrich, Poole, UK, were dissolved in chloroform to give concentrations (w/v) of 0.2% rifampicin, 1% trimethoprim and 1% triclosan. The silicone tubing was immersed in the solution at room temperature for 1 h, during which it swelled to approximately twice the original volume. The tubes were then removed, briefly rinsed in ethanol and air-dried overnight during which they returned to their original dimensions. During this time the molecules of antimicrobial are dispersed evenly throughout the silicone matrix. Antimicrobial and plain tubing controls were packaged and sterilized by autoclaving at 121°C for 15min.

2.3. Test bacteria

A. baumannii isolates used in this study were from cases of EVD ventriculitis at Queen's Medical Centre in Nottingham, UK (F1865); a gift from Dr Mark Enwright, University College Hospital, London, UK (F2653); and a gift from Sheba Medical Centre, Ramat Gan, Israel (F3859). They were characterised by conventional methods: Gram stain, oxidase test, biochemical profiling (API 20NE, BioMérieux, Basingstoke, UK) and growth at 44°C. Matrix Assisted Laser Desorption Ionization Time-of-Flight (MALDI-TOF) technology was used to confirm the phenotypic identification. Antibiotic susceptibility was determined using disk diffusion and interpreted following the CLSI criteria. Twelve antibiotics (Oxoid Ltd, Basingstoke, UK) were tested (Table 1). Multidrug resistance was considered when resistance was found in more than two of the following five drug classes: antipseudomonal cephalosporins (ceftazidime or cefepime), antipseudomonal carbapenems (imipenem or meropenem),

amoxicillin/clavulanate, fluoroquinolones (ciprofloxacin), and aminoglycosides (gentamicin).[19]

Minimum inhibitory concentrations (MICs) of rifampicin and trimethoprim were determined using E-test strips (AB Biodisk, Solna, Sweden). MICs and Minimum bactericidal concentrations (MBCs) of triclosan were determined using broth microdilutions in triplicate.

2.4. Biofilm formation assay.

The ability of *A. baumannii* strains to form biofilm was measured using a microtitre plate assay. Overnight suspensions of F1865, F2653 and F3859 prepared in 100% Tryptone Soya Broth (TSB, Oxoid) to early log phase in a 37°C shaker incubator at 190rpm for 4h, were adjusted to A_{490} 0.6. The bacterial suspension was dispensed in 200 µL volumes in 96-well polystyrene microtitre plates and incubated for 24h at 37°C. After removal of the medium, plates were washed twice with phosphate-buffered saline solution (PBS), fixed with 150 µL of methanol and airdried. Biofilm was stained with 150 µL of 2% crystal violet solution for 15 min. After a gentle wash with distilled water, the plates were again airdried before the biofilm-associated dye was solubilised with 150 µL of 100% ethanol. 100 µL of this solution was transferred to a new 96-well microtitre well and the A_{490} of each well was measured using an automated microtitre-plate reader (BioTek ELx800^{TM}). All tests were carried out three times.

2.5 *Measurement of bacterial adhesion to plain silicone*

Tests of attachment were intended to detect any difference between the three strains (F1865, F2653 and F3859), which were grown in 100% Tryptone Soya Broth to early log phase in a 37°C shaker incubator at 190rpm for 4 h. They were then centrifuged for 20 min and re-suspended in a TSB concentration, typically 0.125%, previously determined by experiment for each strain that would allow the bacteria to survive in the medium but not to replicate. Autoclaved plain 1 cm silicone tube segments were immersed in 1:1000 diluted human plasma (NHSBT, Watford, UK) for 1h at 37°C to develop a conditioning film. After rinsing them, they were exposed to the bacterial suspensions, adjusted to A_{490} 0.8-0.9 (10^8 cfu/mL) and then diluted to 10^6 cfu/mL, for 1h at 37°C. Then they were removed and sonicated for 5 min at 50 Hz.

Viable bacteria in the sonicate were enumerated by spreading onto Sheep Blood Agar (Oxoid) and incubating at 37°C for up to 48h.

2.6. Determination of time to kill bacteria (tK100)

The tK100 is designed to determine the time taken to kill 100% of a challenge of bacteria attached to the biomaterial.[20] The bacterial test strains (F1865, F2653 and F3859) were grown in 100% Tryptone Soya Broth (TSB, Oxoid) to early log phase in a 37°C shaker incubator at 190rpm for 4 h. They were then centrifuged for 20 min and re-suspended in a previously determined TSB concentration (0.125%) that would allow each strain to survive in the medium but not to replicate. Human plasma conditioning film was applied as described above. After rinsing, the plasma-coated impregnated segments were exposed for 1h at 37°C to the bacterial suspensions, adjusted to A_{490} 0.8-0.9 (10^8 cfu/mL) and then diluted to 10^6 cfu/mL. They were then rinsed and immersed in dilute TSB concentration and incubated at 37°C. Every day the segments were removed and immersed in fresh dilute TSB. At intervals of 0, 24, 48 and 72 h, three segments of each series were removed and sonicated for 5 min at 50 Hz. Viable bacteria in the sonicate were enumerated by spreading onto Sheep Blood Agar and incubating at 37°C for up to 48h. Plain silicone control 1cm segments were treated exactly the same as impregnated segments.

2.7. In vitro challenge (IVC)

The IVC is designed to determine the ability of impregnated catheter tubing to resist bacterial colonization with multiple bacterial challenges in flow conditions.[18] The apparatus is modular and consists of a series of glass cylinders. The autoclaved test catheter tubes 35 cm length were aseptically introduced through the glass cylinders which were then filled with distilled water. The lumens of the catheters were perfused with 2% TSB from a reservoir by means of a pump at 20 mL/h and this was discharged into a waste collection vessel. The system was maintained in an incubator set at 37°C. F1865, F2653 and F3859 were used to challenge the test and plain tubing controls in triplicate. The test bacteria were grown in 20 mL TSB for 4h on a 37°C shaker incubator set at 190 rpm and the A_{490} adjusted to 0.8-0.9 (10^8 cfu/mL) and then diluted to 10^4 cfu/mL. To challenge the catheters, perfusion was stopped and 1 mL of bacterial

suspension was aseptically inoculated down the catheters. Clamps were applied for 1h to allow attachment. Clamps were then removed and perfusion was re-started. Samples of effluent were aseptically collected periodically from the outlet of the catheters for determination of viable count. The catheters were re-challenged with new controls every 2 weeks if the bacteria had been cleared and there was no evidence of colonization by that time, and this regimen was continued until 42 days. At day 42, the successful impregnated catheters were removed from the apparatus and were aseptically filled with 200 µL of sterile water and clamped at both ends. Then they were sonicated for 5 min at 50 Hz and 100 µL of the lumen sonicate was spread onto Sheep Blood Agar (Oxoid) and incubated at 37°C for up to 48h. Gram stain of the sonicates was also performed.

2.8 Scanning Electronic Microscopy

The surface of the lumens of all the tubing was analysed using a JEOL 6060LV variable pressure scanning electron microscope (SEM). The impregnated tubing which passed the challenges was analysed after 42 days and the ones that failed were analysed when colonisation was detected.

2.9 Statistical analysis

OD readings obtained in the biofilm formation assay were recorded as mean +/- SD and t test was used to compare the strain which produced more biofilm, F2653, with the others. A p value <0.05 was considered to indicate a statistical significance.

Results

3.1. Microorganisms and sensitivities

The susceptibilities of the two *Acinetobacter* strains tested are shown in Table 1. The three strains tested were multidrug resistant. The principal difference in the antibiogram performed was susceptibility to carbapenems of the F1865 strain and resistance to them of F2653 and F3859 strains.

Regarding the antimicrobials used in the impregnated tubing, the three strains were susceptible only to triclosan with a MIC=1mg/L for F2653 and F1865 and MIC =2mg/L for F3859.

3.2 Biofilm formation assay

Summarised data are shown in Figure 1. Strain F2653 produced significantly more biofilm than the F3859 ($p<0.001$) and F1865 ($p<0.001$) strains.

3.3 Measurement of bacterial adhesion to plain silicone

Results are shown in Figure 2. Strains F2653 and F1865 attached better than F3859 to plain silicone segments.

3.4 tK100 assay

Results are shown in Figure 2. Bacterial counts were examined at 0 h, 24h, 48h and 72h. All attached bacteria to the impregnated segments were killed at 48hr in the case of F1865 and F3859, with a 3-log reduction at 24h in F1865. F2653 took 72 hr for 100% kill, with a 4-log reduction at 48h.

3.5. In vitro challenge (IVC)

Results are shown in Figure 3. Impregnated 35cm length tubing was tested against F2653, F1865 and F3859 in triplicate by in vitro challenge. (Figure 3). The three tubes challenged with F1865 passed while one impregnated tube challenged with F2653 become colonised at the end of the second challenge (Day 24). The challenge bacteria were eradicated from the other two impregnated tubes in this set. Of the three impregnated tubes that were challenged with F3859, one failed after the third challenge (Day 29) and one became colonised 12 days later (Day 41).

No bacteria were found after Gram stain and culture for 48h in samples taken from lumens after sonication of successful impregnated tubing.

Isolates from impregnated tubing which failed were analysed by MALDI-TOF and confirmed to be the same strain of *A. baumannii* as their respective inoculum. Upon testing for resistance to triclosan, trimethoprim and rifampicin, the MICs were found to have remained unchanged.

3.6. Scanning electronic microscopy (SEM)

SEM images showed the presence of a large biofilm formation on the lumen of the impregnated tube which failed. However, the SEM images of the impregnated tubes which passed the challenge during 42 days did not show any presence of bacteria (Figure 4).

4. Discussion

Antimicrobial - impregnated EVDs have been reported that contain several combinations, all including rifampicin, targeting on Gram positive microorganisms as staphylococci, have shown efficacy in-vitro and a reduced risk of ventriculitis in clinical trials.[8-11] However, recently MDR enterobacteria have often been involved in nosocomial outbreaks. [24] For this reason, we have developed a new impregnated EVD catheter with antimicrobials active against Gram negative bacilli including MDR enterobacteria without losing the activity against Gram positive microorganisms. Particularly, MDR *A. baumannii* has emerged as a pathogen of concern, over 50% of them being carbapenem-resistant in intensive care units. Its global estimated costs are around USD742 million annually. [25, 26] Consequently, options for antibiotic treatment are limited for EVD-associated *A. baumannii* infections. For these reasons, we have focused on its prevention and specifically investigated the in vitro antibacterial activity of a new impregnated external ventricular drainage catheter, demonstrating that it was able to withstand multiple challenges by MDR *A. baumannii* in constant flow conditions for periods more than sufficient to cover the usual 21day upper limit of drainage time.

The tK100 assay is specifically designed to test the ability of an antimicrobial material to kill 100% of attached bacteria, as these are known to exhibit more phenotypic insusceptibility to antimicrobials than in planktonic mode.[27,28] In order to prevent progression to infection and to prevent resistance developing, it is essential that all attached bacteria are killed. The time taken for these catheters to kill a high inoculum of 10^6 cfu/mL of *A. baumannii* that become attached to their surfaces was

approximately 48h, consistent with previous findings for antimicrobial EVD catheters against staphylococci. These results were achieved despite the high inoculum and a plasma protein conditioning film, the use of which is advisable in order to simulate in-use conditions,

The IVC model has been validated as a clinically predictive test for antimicrobial catheters,[29-31] and is designed to mimic some of the important conditions of an external ventricular drain where the lumen of the catheter may become contaminated during its life in the lateral ventricle, leading to catheter colonisation. Here, the tubing challenged with *A. baumannii* gave a more than 3 weeks of protective activity against repeated high microbial loads challenges with three different strains. Some authors have claimed that CSF culture negative does not exclude presence of viable bacteria in an EVD as the antimicrobials released into the lumen might inhibit their growth.[32] That study was carried out over a very short time scale without flow conditions on a different antimicrobial EVD from the one used here, and we have shown that, over all except Day 1 of EVD perfusion, there is no reduction of bacterial viability for the catheter used in our study. [33] However, as a precautionary measure, we exhaustively evaluated our tubing which passed the IVC test using sonication and SEM to ensure that no attached bacteria remained. Tubing which failed with a positive culture was analysed by SEM and biofilm was found. However, we did not observe an increase in resistance of the surviving strains after exposure to the impregnated tubing.

To our knowledge, no other antimicrobial EVD catheters are commercially available or have been tested for prevention of *A.baumannii* colonization. Only a central venous catheter coated with chlorhexidine, minocycline and rifampicin achieved good results in inhibiting biofilm colonization by various resistant Gram-negative bacteria, including MDR *A. baumannii*. [34] However, this catheter was polyurethane and contained chlorhexidine, which is not suitable for use in the central nervous system.

The correlation between *A. baumannii* ability to adhere and form biofilm, probability to cause outbreaks and life-threatening infections and antibiotic resistance has not been thoroughly evaluated. Among our phenotypically different clinical isolates we found differences in terms of biofilm formation, adherence to silicone and performance in the tk100 assay. Moreover, the IVC model, which is a dynamic model

simulating to some extent the in vivo conditions of EVD, showed that the only "early" failure occurred when tubing was tested with F2653, while tubing tested with F3859 failed after 3 challenges and tubing tested with F1865 did not fail during the test period. Our results suggested that our MDR strain F2653 might have a more virulent behaviour than the other strains, particularly in respect of ability to attach to catheters . The different behaviour we observe in clinical practice, where some strains cause outbreaks and other only colonise the EVDs without causing illness, might be determined by the virulent factors of each strain, as other authors have also been reported. [35]

Toxicity profiles of systemic rifampicin and trimethoprim are well recognised from extensive clinical experience, and they are considered to be safe in routine use, while toxicology of triclosan for other than topical use is less well-known. The agent has been used in antimicrobial absorbable sutures and found not to give rise to inflammatory response. [36-38] Although triclosan has not been used systemically in humans, a dose of 40mg/kg has found to be safe in mice. [39] Triclosan has received very extensive detailed human toxicology study including safe tissue and plasma levels.[40] Further in vivo studies are needed to confirm lack of neurotoxicity in brain tissue, before this formulation can be used for EVD in patients.

In conclusion, results presented here show that the antimicrobial catheters were able to eradicate all *A. baumannii* that had become attached to the catheters, even under flow conditions. The new antimicrobial catheter promises to reduce MDR *A. baumannii* EVD infections over the first 3 weeks of use. Human neurotoxicity of triclosan has not been tested but evidence suggests it is likely to be safe. Moreover, we have shown for first time in a dynamic in vitro model that clonal outbreak strains with different virulence factors such as biofilm formation and silicone adherence might influence outcome in MDR *A. baumannii* ventriculitis. The next step will be confirming lack of neurotoxicity of triclosan in an animal model and then testing the efficacy of the EVD catheter in a human clinical trial.

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RB holds a patent for the process and formulation described. He receives speaker fees from Codman and Shurtleff Inc but not for personal gain, as these are donated to his university.

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Table1a. Susceptibility patterns of *Acinetobacter baumannii* strains F1865, F2653 and F3859. Zone diameter (mm) of our strains and MIC interpretive standards for *Acinetobacter spp*. by CLSI (2012).

	TIC (75)	PRL (75)	AMC (30)	CTX (30)	CAZ (30)	FEP (30)	ATM (30)	MEM (10)	IPM (10)	CIP (5)	CN (10)	CT (25)	CT (10)
F1865	19/I	2	0	0/R	10/R	15/I	15	24/S	24/S	0/R	13/I	15/S	13/S
F2653	0/R	11	0	0/R	15/I	18/S	15	11/R	12/R	0/R	0/R	18/S	15/S
F3859	0/R	0	0	0/R	0/R	9/R	0	0/R	10/R	0/R	0/R	14/S	14/S

Table 1b. Minimum inhibitory concentrations (MICs) in mg/L of the antimicrobials against *Acinetobacter baumannii* strains F1865, F2653 and F3859 and Minimum bactericidal concentrations (MBCs) of triclosan. Interpretation of susceptibility is provided according the literature.[21,22,23]

	MIC Rifampin (mg/L)	*[21]	MIC Trimethroprim (mg/L)	*[22]	MIC Triclosan (mg/L)	*[23]	MBC Triclosan (mg/L)
F1865	3	S/LR	>32	R	1	LR	16
F2653	3	S/LR	>32	R	1	LR	16
F3859	12	R	>32	R	2	LR	>32

Figure 1. Biofilm assay. Strain F2653 produced more biofilm than the F3859 and F1865 strains. A positive and negative control was used.

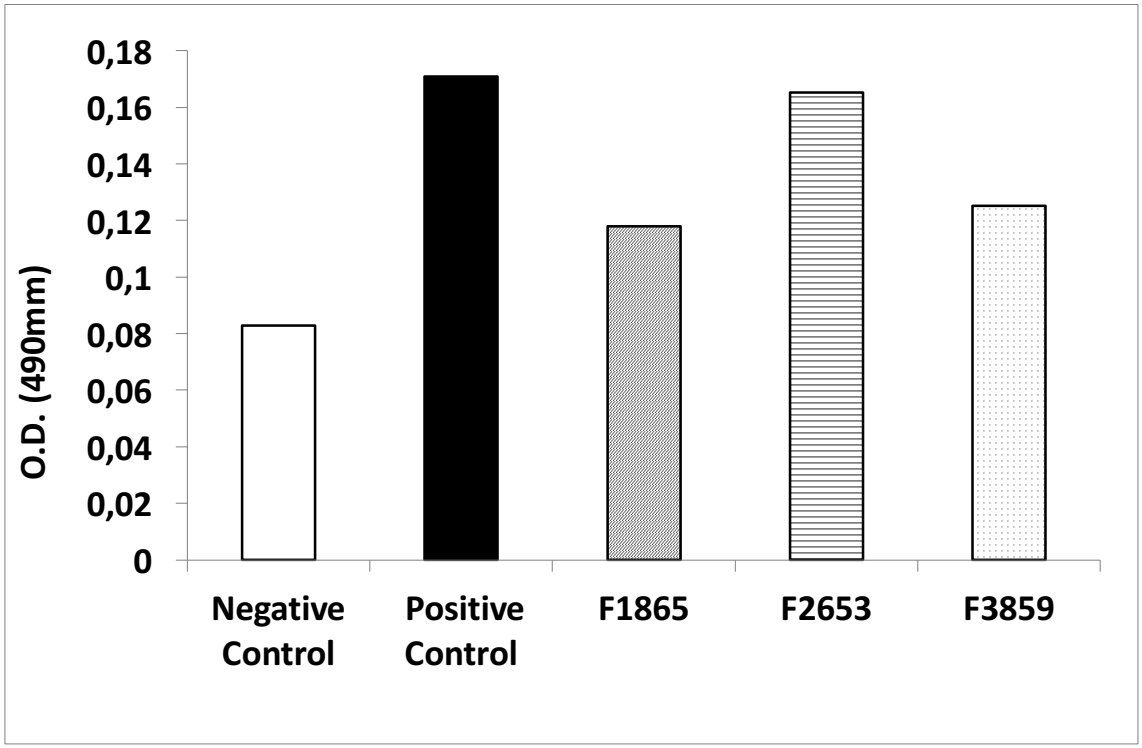


Figure 2. Measurement of bacterial adhesion to plain silicone and time to kill all attached bacteria (tK100) assay

Open and filled circle line represents strain F2653 in plain (control) and impregnated tubing repectively; Open and filled square line represents strain F1865 in plain (control) and impregnated tubing repectively; Open and filled triangle line represents strain F3859 in plain (control) and impregnated tubing repectively;

After 1h inoculation (black syringe) of 10^6 cfu/ml of strains of *Acinetobacter baumanii* (F2653, F1865 and F3859), attachment to plain silicone was measured. Eradication to 1cm plain and impregnated tubing was measured every 24h for 72h. Measurments were made in each strain and in both plain (control) and impregnated tubing.

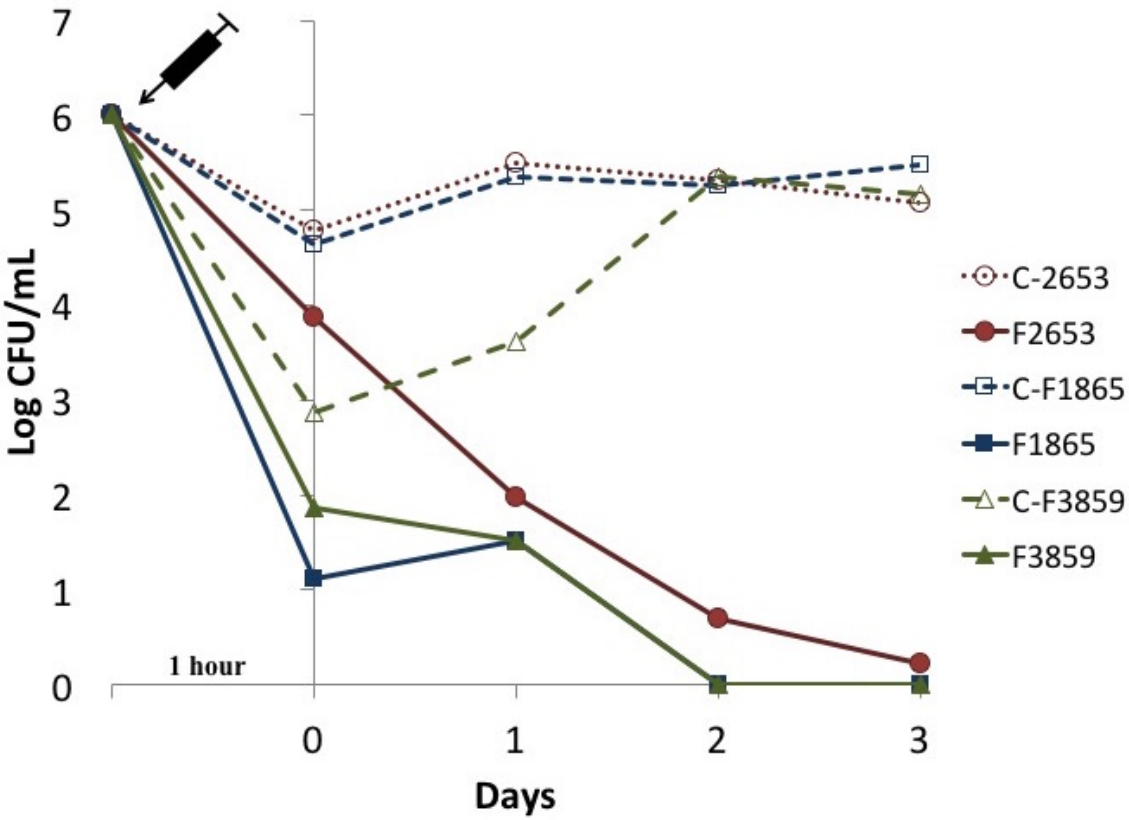
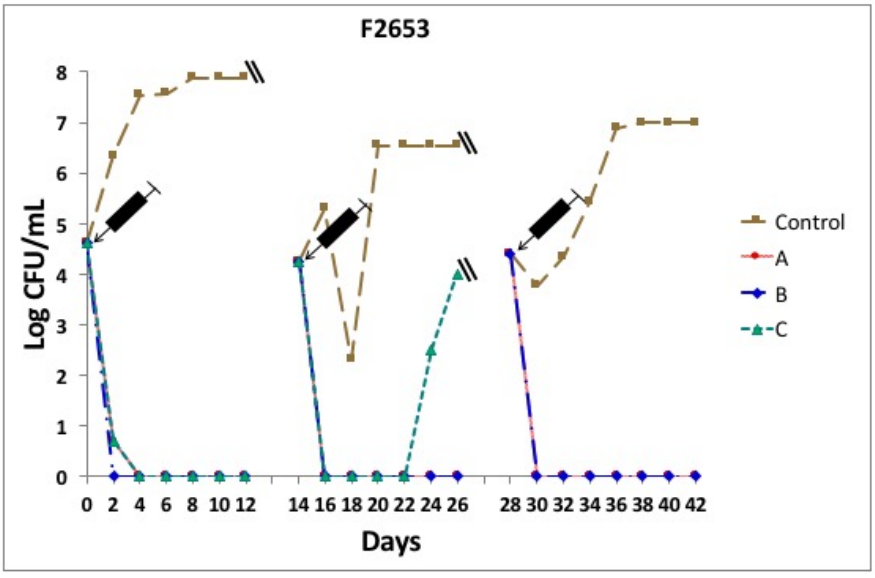
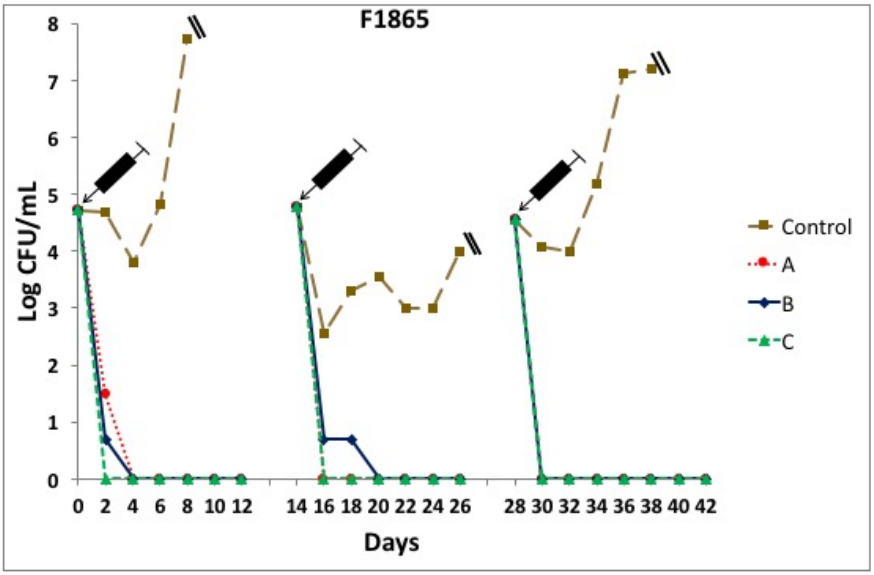


Figure 3. Inoculation of 10^4 cfu/mL of *Acinetobacter baumanii* F2653 (a), F1865 (b) and F3859 (c) was done on day 0 and every 14 days (black syringe). Three impregnated catheters (A, B, C) and one plain control catheter were challenge with each strain (in total 9 impregnated catheters and 3 controls). Filled square patterned line represents control plain catheter; Filled circle patterned line represents impregnated catheter A; Filled diamond solid line represents impregnated catheter B; Filled triangle patterned line represents impregnated catheter C. Bacterial counts were measured daily at the sampling point. Removal of EVD plain control catheter was performed before every new challenge at 14 and 28 day. Removal of EVD impregnated catheter if failure. Removal was marked with two parallel lines for both impregnated and control catheters.
Several lines are superposed in the figure due to most of the impregnated catheters showing similar pattern of bacterial eradication.

a.



b.


F1865
Log CFU/mL
Days
Control
A
B
C

c.

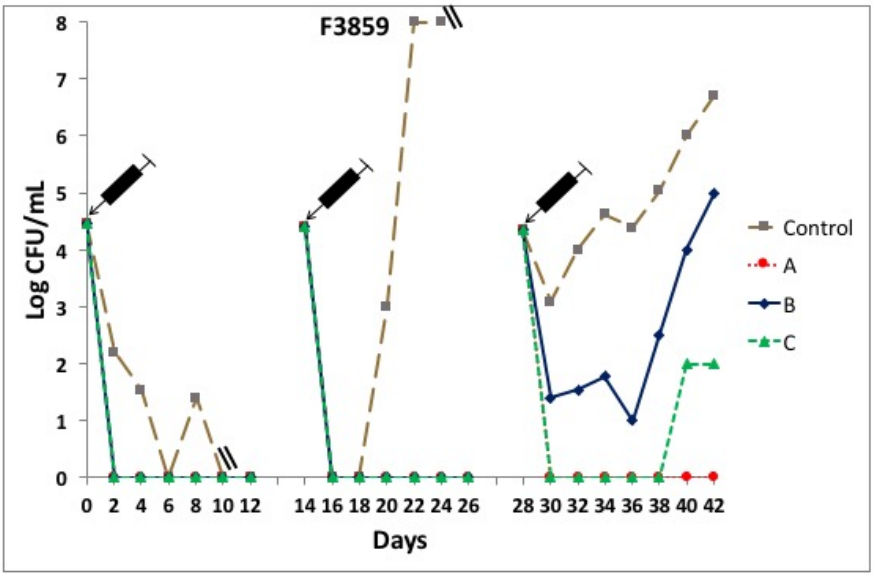
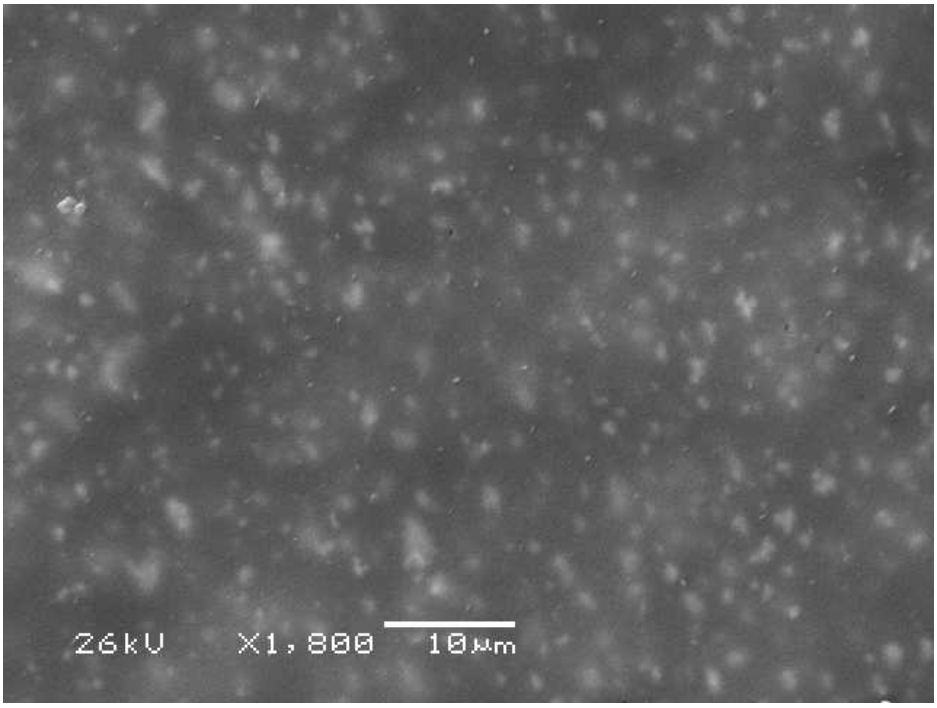
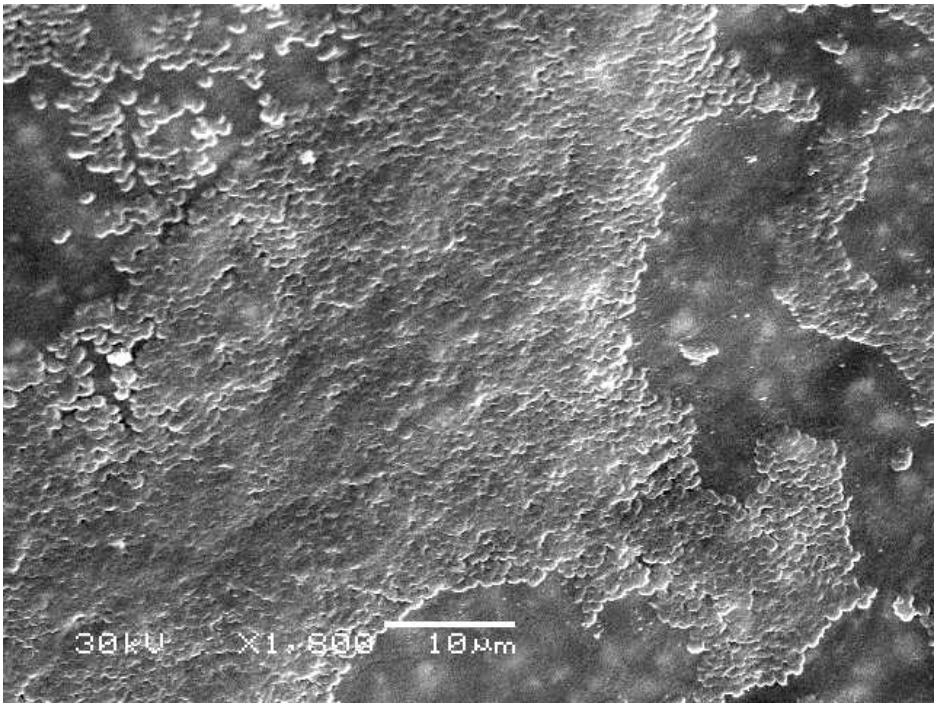

F3859
Log CFU/mL
Days
Control
A
B
C

Figure 4. Scanning Electronic Microscopy: Lumen of impregnated catheter (a) which passed the challenges was analysed after 42 days and the impregnated catheter (b) that failed showed bacterial colonisation.

a.



b.



DISCUSSION

1. Hydrocephalus complicating community-acquired bacterial meningitis

Substantial progress has been made in the last 20 years in the prevention and treatment of C-ABM (5). Implementation of vaccines, development of new ones, the widespread use of anti-inflammatory treatments, and early initiation of the appropriate antibiotic treatment in patients with C-ABM have decreased the disease burden (112). However, C-ABM remains one of the most feared infectious diseases worldwide and is associated with substantial mortality and long-term neurological complications.

Neurological complications in C-ABM are frequent and represent the major determinants for a lethal outcome, with the exception of meningococcal sepsis. The identification of these complications and their time of expected occurrence may help to develop additional treatment regimens in C-ABM in adults.

Hydrocephalus complicating C-ABM is historically one of the least explored complications of this disease. The few studies published to date (29, 43-46) estimate the occurrence to be between 3% and 21%.

The first study included in this thesis is the first Spanish study (and the fifth worldwide) of adults with hydrocephalus complicating C-ABM. With our 22 patients presenting hydrocephalus out of our historical cohort of 790 episodes of C-ABM, we estimate the occurrence of hydrocephalus complicating C-ABM in our area to be 3%, similar to the rates reported in European studies (3-5%) (43, 45). Patients with hydrocephalus were at a significantly higher risk of unfavourable outcome: mortality and neurologic sequelae rates were 50% and 55% respectively, in comparison with corresponding rates of 13% and 14% in patients who did not develop hydrocephalus. The causes of death were found to be herniation and other neurological complications. Taking this into account, optimal management must be provided, comprising early detection of hydrocephalus and appropriate treatment.

The timing of the diagnosis of hydrocephalus varies from series to series. In the study in Taiwan (44), 100% of patients were diagnosed at admission, while in a German cohort (29) most of the patients were diagnosed in the first two weeks and only 17% at admission. In our study, 46% of patients were diagnosed at admission, a figure closer to the 69% diagnosed at admission in the Dutch cohort (43). The differences in the

times of diagnosis may depend on the time patients consult; it is the patients who develop hydrocephalus during admission in whom our intervention might have an impact.

Therefore, in order to expand our knowledge of hydrocephalus complicating C-ABM we performed an analysis of the risk factors for developing the condition and identified age, time to illness > 48h and *L. monocytogenes* as independent risk factors. Unfortunately, these are factors that we cannot modify but they can help us to identify populations who are at risk of developing hydrocephalus and thus follow them up more closely. Age and a long time to illness are factors that increase the likelihood that patients suffering C-ABM will not achieve CSF resorption due to arachnoid granulations, thus raising the risk of hydrocephalus. While we cannot modify the long pre-admission period of the disease, suspicion and careful management of hydrocephalus may influence the clinical prognosis.

In a European controlled trial in C-ABM (22), adjuvant treatment with dexamethasone was associated with a reduction in mortality, especially in *S. pneumoniae* (34 to 14%). Since 2002, it has been widely recommended in treatment of C-ABM, although in our hospital it was already in use in 1987. Based on animal studies, which suggested a benefit of steroids in preventing hydrocephalus (113), we specifically analysed the influence of dexamethasone on the development of hydrocephalus complicating C-ABM, but did not find a significant difference in its development between episodes of C-ABM which received adjuvant dexamethasone and those which did not. However, in the subgroup of patients with pneumococcal meningitis we observed a trend towards a decrease in the rate of hydrocephalus (2%) in comparison with those patients who did not receive dexamethasone (7%). We have only found comparable data in two Danish cohorts (45, 46). The first one agrees with our hypothesis because the patients who developed hydrocephalus did not receive dexamethasone, while 30% of those who did not receive the drug developed the condition. The second one concluded that use of dexamethasone was not a protective factor for mortality, although no exact data on the outcome of patients receiving dexamethasone were provided. In previous clinical studies no evidence of any benefit of adjuvant dexamethasone in preventing hydrocephalus has been reported although it has not been investigated in a specific

study, for several reasons: the German (29) and Taiwanese (44) cohorts were not able to do so as adjuvant dexamethasone was not in standard use at the time of the studies; in the Dutch cohort (43) all patients received adjuvant dexamethasone, and the comparison was not possible.

A range of approaches to management of hydrocephalus complicating C-ABM have been proposed. The Dutch study (43) suggested that neurosurgical procedures in hydrocephalus complicating C-ABM might be deleterious, as all their patients who underwent a neurosurgical procedure had a poor outcome. These authors point out that similar rates of mortality (50%) had been found in previous cohorts with higher rates of procedures performed, thus supporting conservative management. In our cohort, nine patients underwent treatment for hydrocephalus with a mortality rate of 56%, regardless of the procedure. Although mortality was lower in patients who did not require neurosurgical procedures (46%), we think that this might have been due to a selection bias; patients who were critically ill were “forced” to receive an EVD and had a lethal outcome due to their inner state. Although it is true that some patients develop reversible hydrocephalus and do not need an EVD to solve it, we lack sufficient evidence of the indication of neurosurgical devices in the management of this complication, and so careful discussion of each case with the neurosurgery team is required.

As in the previous largest cohort published, *S. pneumoniae* and *L. monocytogenes* were the more prevalent aetiologies in our series. Patients with pneumococcal meningitis are at risk of intracranial complications and unfavourable outcome, but interestingly we identified *L. monocytogenes* as a common cause of hydrocephalus complicating C-ABM. When we reviewed separately the 59 episodes of LMME, including episodes of *L. monocytogenes* rhombencephalitis, we found that communicating hydrocephalus was a frequent complication of LMME in our series (14%). The reason why *L. monocytogenes* causes hydrocephalus might be related to the time to presentation since the frequency of hydrocephalus among our patients with symptoms for >4 days was higher than 30%. It is not often diagnosed at admission, as the CT scan appears normal, and its detection in our patients was delayed for a median of six days after admission.

This thesis also addresses controversial aspects related with *L. monocytogenes,* the third most common cause of C-ABM in adults. Because of their link to hydrocephalus and the recent increase in LMME we collected a large series of LMME episodes homogeneously recorded at a single centre, including those diagnosed not only by CSF culture but also by positive blood culture for *L. monocytogenes* and CSF pleocytosis, thus offering a more complete perspective of the disease than other reported series (33, 59, 114).

First of all, our findings corroborate the recent increase in LMME reported by other authors worldwide (1, 32, 52, 115, 116) who now rank *L. monocytogenes* as the third most common cause of C-ABM in adults, following pneumococcal and meningococcal meningitis.

Secondly, we performed a detailed analysis of factors involved in short-term mortality and sequelae. Overall mortality in our series was high (24%), in the middle of the reported range in recent cohort studies (17–36%) (32, 33, 52, 59). Time and causes of death are issues that are not well defined in the literature. Mortality was defined as early in a third of our patients, due to neurological causes (60%), mostly seizures, and systemic complications (40%), and late in the other two-thirds, due to neurological complications, mainly caused by hydrocephalus. The analysis of risk factors for mortality in LMME identified inappropriate empirical antibiotic therapy and hydrocephalus as the main independent prognostic factors.

This identification of inappropriate empirical antibiotic therapy as a risk factor for mortality is a relevant finding, which has not described previously in other cohorts of LMME patients. The recently published ESCMID guideline on diagnosis and treatment of acute bacterial meningitis strongly recommends starting antibiotic therapy as soon as possible, and states that the time period until antibiotics are administered should not exceed 1 h (14). Therefore, physicians should always consider adding ampicillin to cephalosporin when C-ABM is diagnosed in the emergency room without aetiological confirmation in patients over 50 years of age. Furthermore, we recommend adding ampicillin in patients of all ages with suspected C-ABM of unknown focus and without petechial rash, especially in those with immunosuppression.

Other potentially relevant factors not clearly associated with LMME patient outcome, such as definitive antimicrobial treatment choice, adjuvant therapy and seizures also merit discussion.

We found no differences in mortality between the group treated with high doses of ampicillin alone for 21 days and the group treated with ampicillin plus amino-glycosides. Although combination therapy has been established as the recommended treatment for LMME (31, 50, 55, 117), some authors have suggested higher mortality among patients treated with aminoglycosides, arguing that this treatment should be avoided due to its toxicity and its unclear beneficial effect (32, 52, 56). Nevertheless, a very recent French study of listeriosis (57) supports combination treatment. Given the practical difficulties involved in completing clinical trials in listeriosis, our data support the idea that combined treatment should be considered as the first-line combination in LMME patients. We think that a short course of 5–7 days of aminoglycosides added to ampicillin may provide a sufficient synergistic effect without causing relevant side effects.

Our data suggest that use of adjuvant dexamethasone or phenytoin in a subgroup of these patients may have a benefit, but more evidence is needed to confirm this hypothesis. The role of dexamethasone in LMME is not well defined, as immunocompromised patients were not included in the Dutch clinical trial (22) which showed improved outcome in C-ABM when dexamethasone was administered as an adjuvant treatment. However, guidelines and new studies recommend its withdrawal after isolation of *L. monocytogenes* (57, 59) due to a lack of evidence of any beneficial effect (14). Moreover, a recent report of neurolisteriosis in a French cohort (57) suggested a deleterious effect. However, although we could not demonstrate any useful effect of dexamethasone administered for two days in preventing hydrocephalus in our clinical series, it proved to be safe. In our center, we administer dexamethasone as adjuvant treatment in a smaller doses (4 mg of dexamethasone every 6h for 48h) than in these studies (10mg every 6h for 4 days), and it might influence on the different outcome. In any case, the possibility that dexamethasone

might have some protective effect in avoiding or modifying the development of hydrocephalus in a particular group of patients with LMME cannot be totally ruled out.

Interestingly, we observed fewer neurologic sequelae in patients receiving adjuvant therapy with dexamethasone. In our study, rhombencephalitis occurred in roughly 20% of cases of LMME as a more subacute form of the disease, associated with focal disease and with more frequent sequelae. *L. monocytogenes* rhombencephalitis has rarely been analysed separately from meningitis and the clinical form of presentation has not been evaluated as a prognostic factor in previous case series (54, 118).

Seizures occur frequently in C-ABM (15–24%) (1, 28, 29), especially in pneumococcal meningitis (28%) (30), and are associated with increased mortality (41%) (28). For this reason, since 1987, anti-seizure prophylaxis with phenytoin has been systematically administered at our centre when pneumococcal meningitis was suspected, with good results (119). In the present series of LMME, 12% of elderly patients with underlying diseases and 29% of those with coma at admission who did not receive anti-seizure prophylaxis suffered from seizures; other studies have reported similar results (7–17.1%) (31-33). In addition, a trend towards a higher neurological mortality was observed in this group. While anti-seizure prophylaxis was not identified as a protective factor for mortality, no seizures were observed among the 13 patients receiving this adjuvant therapy. No information is available on the use of anticonvulsants in patients with LMME, so we think that they could be considered in elderly patients with low levels of consciousness at admission.

The major limitation of these studies is that CT was not performed systematically at admission, meaning that hydrocephalus may have been underdiagnosed; furthermore, the fact that adjuvant (dexamethasone and phenytoin) and antibiotic treatment were not administered in a randomized fashion to all patients influenced the assessment of the real effect of these drugs.

2. Treatment of infection of CSF devices used for hydrocephalus

Infection associated with a foreign body usually requires its removal in order to achieve cure (120). This is so not only in the setting of VP shunts, but in the case of other biofilm-associated infections such as prosthetic joint infection or pace-maker-infection.

The third study included in this thesis was carried out in the largest cohort of adults with VP shunt infection reported to date. It was designed to evaluate the impact on outcome of different treatment strategies, focusing on CSF sterilization, mortality, and superinfection. Almost all our patients were treated using a strategy that combined antibiotic and surgical treatment, and the main conclusion was that management, including VP shunt retention, was the only statistically significant predictor of failure.
A potential limitation of our study is that the decision to choose a first-line strategy or to start salvage therapy did not follow a defined protocol, a circumstance that may have biased our treatment groups and consequently our results. However, a clinical trial in this setting would be difficult to perform.

When a VP shunt infection is diagnosed, the treatment strategy must be decided upon immediately and the need for the VP shunt must be reconsidered. Among patients who are not CSF shunt dependent, shunt removal is, without doubt, the preferred strategy; the clinical challenge lies in the treatment of patients who do need the CSF shunt. Treatment with OA alone is discouraged by the low cure rate in previous cohorts (75, 76, 121, 122) and confirmed in our series, although further research using new antibiotics is required (123-125).

TSSR was the most successful strategy, with a cure rate of 89%, similar to the rates reported in previous studies (66, 67, 82, 126). In addition, TSSR presented low mortality (8%) and the highest CSF sterilization rate (95%).
Many patients undergoing TSSR may need an EVD/ELD, which may lead to a worse outcome. However, the complications, including superinfection of the EVD/ELD, did not require any important diversion from the treatment plan and did not lead to fatal

outcomes in our study. A difficult decision for neurosurgeons, and an unresolved problem in attempting TSSR, is to establish the ideal time between the removal of the infected VP shunt and the placement of a new one in order to guarantee cure. In our experience, second-step surgery was performed after a median of 17 days, a period in the low range according to previous reports (66, 67). However, in 25% of our episodes managed with TSSR, the VP shunt was replaced within 12 days with no relapse. In these episodes, a CSF culture sample was taken through a different drainage catheter during the first surgical procedure, and antibiotic treatment was administered until the results were available. If negative, the new VP shunt was inserted safely and rapidly.

In contrast to the results with TSSR, outcome in our patients managed with OSSR was poor; the cure rate was 33%, much lower than the 88% reported in a similar series of adult CSF shunt infection (66).

These differences may be partially due to methodological and inclusion criteria. For example, half of our episodes could not actually have their VP shunt exchanged due to lack of CSF sterilization or blockages while the peritoneal catheter was being externalized. This is a situation that reflects the real likelihood of failure when CSF sterilization with intravenous antibiotics is attempted. In addition, the number of Gram-negative bacilli infections, assumed to be associated with a worse outcome (127), was higher in our series. However, in the OSSR group in whom the VP shunt replacement was finally performed the cure rate was 60%, similar to the rates reported in other paediatric cohorts (121, 122, 128). In any case, it is important to note that some patients who appeared to have CSF sterilization at the time of VP shunt replacement relapsed after surgery. In fact, in patients in whom OSSR failed, the replacement was performed a median of 11 days earlier than in those in whom it succeeded. On the other hand, superinfection of the externalized peritoneal catheter occurred in 21% of OSSR patients within a median time of 18 days. In our opinion, if OSSR is chosen, absolute CSF sterilization must be confirmed before replacement, and the time of peritoneal catheter externalization while the patient receives antibiotics must be weighed against the critical risk of superinfection. Episodes treated with OSSR presented significantly longer hospital stays than those treated with TSSR, leading to higher overall costs.

We cannot be certain that OSSR and OA would not have led to a higher and faster CSF sterilization rate if antimicrobial therapy had been optimized using systemic antibiotics with a higher bactericidal profile, such as daptomycin or rifampin and/or intraventricular antibiotics. Addition of rifampin to the staphylococcal VP shunt infection treatment without shunt removal seemed to be effective in selected patients (66, 129). Although only a small number of our patients received rifampin, our data also suggest a better outcome for patients treated with a rifampin-based combination. While the role of intraventricular antibiotics remains controversial (130-131), one report has claimed success in selected patients with CoNS shunt infections with a functioning system using intraventricular vancomycin plus systemic rifampin without shunt removal (129). Unfortunately, in our limited experience, we did not identify any differences in prognosis.

In summary, VP shunt removal, particularly TSSR when the patient is shunt-dependent, remains the optimal choice of treatment of VP shunt infection in adults and does not increase morbidity. OSSR and OA had a high failure rate and, if chosen, require careful management and an optimized antimicrobial schedule.

3. Prevention of infection of CSF devices used for hydrocephalus

Multi-drug resistant enterobacteria have often been implicated in nosocomial outbreaks, including CSF devices infections (132). Particularly, MDR *A. baumannii* have emerged as pathogens of concern, since over 50% are carbapenem-resistant in intensive care units; therefore, few antibiotic options are available for EVD-associated infections by *A. baumannii* and the economic and personal costs are high.

One of the most frequently studied interventions to prevent CSF shunt infections in recent years has been the use of antibiotic-impregnated systems. Particularly, EVDs impregnated with rifampicin plus either clindamycin or minocycline, targeting exclusively Gram-positive microorganisms, have shown efficacy *in vitro* and a reduced risk of ventriculitis in clinical trials (95-98). Consequently, we have developed a new impregnated EVD catheter with rifampicin, trimethoprim and triclosan, which is active against Gram-negative bacilli including MDR enterobacteria without losing its activity against Gram-positive microorganisms. To our knowledge, no other antimicrobial EVD catheters are commercially available or have been tested for prevention of *A. baumannii* colonization.

The last study included in this thesis specifically evaluated the *in vitro* antibacterial activity of a new impregnated EVD catheter. It demonstrated that the device was able to eradicate all MDR *A. baumannii* that had become attached to the catheters, even under flow conditions for periods more than sufficient to cover the usual 21-day upper limit of drainage time.

A preliminary *in vitro* assay was performed before testing the new catheter in a dynamic *in vitro* model. The tK100 assay is specifically designed to test the ability of an antimicrobial material to kill 100% of attached bacteria, as these are known to exhibit more phenotypic insusceptibility to antimicrobials than in planktonic mode (133-134). In order to prevent progression to infection and the development of resistance, it is essential that all attached bacteria are killed. The time taken for these catheters to kill a high inoculum of 10^6 cfu/mL of *A. baumannii* that become attached to their surfaces was approximately 48h, consistent with previous findings for antimicrobial EVD catheters against staphylococci. The *in vitro* challenge model has been validated as a clinically predictive test for antimicrobial catheters (108, 135, 136), and is designed to

mimic some of the important conditions of an external ventricular drain where the lumen of the catheter may become contaminated during its life in the lateral ventricle, leading to catheter colonization. Here, the tubing challenged with *A. baumannii* gave more than three weeks of protective activity against repeated high microbial load challenges with three different strains. To confirm our results, we exhaustively evaluated our tubing, which passed the *in vitro* challenge test using sonication and scanning electron microscopy to ensure that no attached bacteria remained. Tubing which failed the test and had a positive culture was analysed by scanning electron microscopy, which identified biofilm.

The performance of these experiments with three different strains of *A. baumannii* increases the value of our observations; they identify interesting differences between our isolates and allow the study of aspects of pathogenicity.

The correlation between the ability of *A. baumannii* to adhere and form biofilm, the probability of its causing outbreaks and life-threatening infections and antibiotic resistance has not been thoroughly evaluated. Among our phenotypically different clinical isolates we found differences in terms of biofilm formation, adherence to silicone, and performance in the tk100 assay and the *in vitro* challenge model. Our results suggested that our MDR strain F2653 might have a more virulent behaviour than the other strains, particularly with regard to its ability to attach to catheters. The different behaviour we observe in clinical practice, where some strains cause outbreaks and others only colonize the EVDs without causing illness, might be determined by the virulent factors of each strain (137).

Further *in vivo* studies are needed to confirm the lack of neurotoxicity in brain tissue before this formulation can be used for EVD in patients. Toxicity profiles of systemic rifampicin and trimethoprim are considered to be safe in routine use; although neurotoxicity of triclosan has not been tested, the evidence suggests it is also likely to be safe (138-141).

In conclusion, the new antimicrobial catheter promises to reduce MDR *A. baumannii* EVD infections over the first three weeks of use. Moreover, we have shown for the first time in a dynamic *in vitro* model that clonal outbreak strains with different virulence factors such as biofilm formation and silicone adherence might influence outcome in MDR *A. baumannii* ventriculitis. The next step will be confirming the lack of neurotoxicity of triclosan in an animal model and then to test the efficacy of the EVD catheter in a human clinical trial.

CONCLUSIONS

(according to aims)

A. Hydrocephalus complicating community-acquired bacterial meningitis

A.1. Hydrocephalus in adults with C-ABM.

Aim 1. To evaluate the occurrence, clinical characteristics and treatment of patients with hydrocephalus-complicating C-ABM.

1.1. Hydrocephalus complicated C-ABM in 3% of cases, and 41% required neurosurgical procedures.

Aim 2. To measure the impact of complicating hydrocephalus on the outcome of patients with C-ABM.

2.1. Hydrocephalus was related to worse outcome in C-ABM adult patients.

2.2. Overall mortality and neurologic sequelae rates were 50% and 55% respectively and were higher in the hydrocephalus C-ABM group than in the non-hydrocephalus group.

Aim 3. To determine risk factors for development of hydrocephalus complicating C-ABM.

3.1 Hydrocephalus complicating C-ABM was related to age; it was more frequent in those who presented a time to illness >48h and in *L. monocytogenes* meningoencephalitis.

3.2 Use of dexamethasone did not statistically influence the development of hydrocephalus in C-ABM.

A.2 *L. monocytogenes* meningoencephalitis.

Aim 1. To evaluate the efficacy of antibiotic and adjuvant therapy in LMME patients.

1.1. Addition of aminoglycosides to ampicillin did not worsen outcome in our cohort.

1.2. Use of adjuvant dexamethasone or phenytoin in a subgroup of these patients might have a benefit, but more evidence is needed to confirm this hypothesis.

Aim 2. To analyse the risk factors for mortality and sequelae in LMME patients.

2.1 Inappropriate empirical antibiotic therapy and the presence of hydrocephalus were the main risk factors for mortality.

2.2 Rhombencephalitis and focal disease were the main prognostic factors for sequelae.

2.3 The outcome may be improved by means of appropriate empirical antibiotic therapy, suspicion, and careful management of hydrocephalus.

B. Prevention and treatment of infection of CSF devices used for hydrocephalus

B.1. Management of VP shunt infections in adults.

Aim 1. To assess the efficacy of the treatment strategies in an adult cohort of VP shunt infections

1.1 Ninety-three per cent of episodes were treated with a strategy combining antibiotic and surgical treatment.

1.2 VP shunt removal, particularly TSSR when the patient is shunt-dependent, remains the optimal treatment and does not increase morbidity.

1.3 OSSR and OA had a high failure rate and, if chosen, require careful management and an optimized antimicrobial schedule.

Aim 2. To identify risk factors predicting treatment failure in the treatment of VP shunt infection.

2.1. The only independent risk factor for treatment failure was retaining the VP shunt, regardless of the strategy chosen.

B.2. Prevention of EVD-associated infections

Aim 1. To assess the *in vitro* antibacterial activity of a new impregnated external ventricular drainage catheter against MDR *A. baumannii.*

1.1 The antimicrobial catheters impregnated with triclosan, rifampin and trimethoprim were able to eradicate all *A. baumannii* bacteria which had become attached to the catheters, even under flow conditions.

1.2 The new antimicrobial catheter promises to reduce MDR *A. baumannii* EVD infections over the first three weeks of use, and is able to avoid ventriculitis during its short life.

1.3 The antimicrobial catheters were successfully tested with three different strains with different virulence factors.

1.4 The three strains tested showed differences in biofilm production and attachment to silicone, which might influence outcome in MDR *A. baumannii* ventriculitis.

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ANNEXES

Annexe I

Standardized protocol gathering data of C-ABM in the Infectious Diseases Department, Hospital Universitari de Bellvitge, Barcelona

Bellvitge Hospital

Institut Català de la Salut

Servei de Malalties Infeccioses

NHC

Cognoms

Nom

Protocol de meningitis comunitàries

Servei asistencial responsable

Metge responsable

Data de compliment del questionari

Bellvitge Hospital

Institut Català de la Salut

Servei de Malalties Infeccioses

Protocol de meningitis comunitàries

1. Nº d' identificació…….. ☐☐☐☐

2. Meningitis…….. ☐

No 1 ☐ si 2 ☐

3. Serogrup (pel meningococ)…… ☐

A ☐ B ☐ C ☐ Y ☐ W ☐ Altres ☐

4. Etiologia…… ☐☐

5. Núm. d'història…… ☐☐☐☐☐☐☐☐

6. Edat…….. ☐☐

7. Sexe…… ☐

Home 1 ☐ dona 2 ☐

8. Data de diagnòstic (PL)…… ☐☐ ☐☐ ☐☐

9. Adquisició……..Extrahospitalària ☐ ☐

10. Malaltia de base (1)…… ☐☐

11. Malaltia de base (2)…….. ☐☐

12. Malaltia de base (3)…… ☐☐

13. Meningitis recurrent…… ☐

No 1 ☐ si 2 ☐

14. Antecedents epidemiológics…….. ☐

No 1 ☐ si 2 ☐

15. Focus d'origen…….. ☐☐

No en té……..…1 ☐
Fístula probable……...4 ☐
Fístula demostrada…..5 ☐
Sinusitis crónica……...6 ☐
Sinusitis aguda……..…7 ☐
Otomastoiditis crónica.8 ☐
Otitis mitja aguda ……9 ☐

Focus urinari……..…14 ☐
Focus intraabdominal…..…15 ☐
Pneumònia i altres pul……16 ☐
Endocarditis…….17 ☐
Cutáni-mucosos……..18 ☐
Abcés epi-subdural……..…20 ☐
Abcés cerebral…….21 ☐
Altres…….....24 ☐

16. Tractament antibiòtic previ…… ☐

No 1 ☐ si 2 ☐

17. Resum Història Clínica .....

……

……

.....

CLÍNICA

18. Durada malaltia…… <12 h 1 ☐ ☐
12-48 h 2 ☐
2-4 d 3 ☐
>4 d 4 ☐

19. Catarro de víes altes……..... ☐

No 1 ☐ si 2 ☐

20. Odinofàgia…… ☐

No 1 ☐ si 2 ☐

21. Febre >38º (en algun moment)…….. ☐

No 1 ☐ si 2 ☐

22. Febre ucies >38º……. ☐

No 1 ☐ si 2 ☐

23. Esgarrifances……. ☐

No 1 ☐ si 2 ☐

24. Hipotensió……

no 1 ☐ ☐
Hipotensió 2 ☐
Shock 3 ☐

25. Cefalea……. ☐

No 1 ☐ si 2 ☐

26. Rigidesa de clatell……. ☐

No 1 ☐ si 2 ☐

27. Náusees-vòmits……..... ☐

No 1 ☐ si 2 ☐

28. Lesions cutánies……... ☐

No en té 1 ☐ Equimosi 4 ☐
Máculo-papules 2 ☐ Vesículo-pústules 5 ☐
Petequies 3 ☐

AFECTACIÓ NEUROLÒGICA

29. Concencia (en començar el tto)……. ☐

Alerta 1 ☐
Obnubilació 2 ☐
Coma respon al dolor 3 ☐
Coma arreactiu 4 ☐

29 b Glasgow……. ☐☐

30. Focalitat parells…… ☐

No….1 ☐ VI…. 2 ☐ VII….3 ☐ VIII…4 ☐ III…5 ☐ Diversos…..6 ☐

31. Hemiparesia…… ☐

No	1 ☐	Aparició 24-72 h	4 ☐
Aparició abans tt	2 ☐	Aparició 72h-1setm	5 ☐
Aparició les 24h	3 ☐	Aparició >1setm	6 ☐

32. Convulsions…….. ☐

No	1 ☐	Aparició 24-72h	4 ☐
Aparició abans tto	2 ☐	Aparició 72h-1set	5 ☐
Aparició les 24h	3 ☐	Aparició >1set	6 ☐

33. Edema de papila…… ☐

No 1 ☐ si 2 ☐

34. Altra afectació NRL…… ☐

No 1 ☐ si 2 ☐

BACTERIOLOGIA

35. Hemocultiu (abans de tt antibiòtic)…….. ☐

No realitzat	0 ☐
Negatiu	1 ☐
Positiu	2 ☐

36. Frotis faringi (Thayer-Martin abans tractament)……..... ☐

No realitzat	0 ☐
Negatiu	1 ☐
Positiu	2 ☐

37. Cultiu altres (especificar)……. ☐

No realitzat	0 ☐
Negatiu	1 ☐
Positiu	2 ☐

38. CIM Penicil·lina…….…… ☐

0’03	1 ☐	2	7 ☐
0’06	2 ☐	4	8 ☐
0’12	3 ☐	8	9 ☐
0’25	4 ☐	16	10 ☐
0’50	5 ☐	32	11 ☐
1	6 ☐	64	12 ☐

39. CIM Cefotaxima…… ☐

0’03	1 ☐	2	7 ☐
0’06	2 ☐	4	8 ☐
0’12	3 ☐	8	9 ☐
0’25	4 ☐	16	10 ☐
0’50	5 ☐	32	11 ☐
1	6 ☐	64	12 ☐

40. LCR (1) aspecte……..……..... ☐

Clar 1 ☐ Purulent 4 ☐
Opalescent 2 ☐ Hemorràgic 5 ☐
Tèrbol 3 ☐

41. LCR (1) pressió……... ☐☐

42. LCR (1) cèl·lules…… ☐☐☐☐☐

43. LCR (1) fórmula (segm)……..…… ☐☐

44. Hipoglicorràquia(1)……. ☐

No 1 ☐ si 2 ☐

45. LCR (1) proteines……..…….. ☐

<1g 1 ☐ 5-10g 3 ☐
1-5g 2 ☐ >10g 4 ☐

46. LCR (1) gram…… ☐

Negatiu…… 1 ☐
Positiu…….. 2 ☐
Errada interpretació…… 3 ☐

47. LCR (1) cultiu……..…… ☐

Negatiu 1 ☐ Positiu 2 ☐

47bis Ag pneumococ LCR..... ☐

Negatiu 1 ☐ Positiu 2 ☐ No realitzat 3 ☐

47tris Ag pneumococ orina…… ☐

Negatiu 1 ☐ Positiu 2 ☐ No realitzat 3 ☐

48. LCR (2) dia…… ☐☐

49. LCR (2) aspecte…….. ☐

Clar 1 ☐ Purulent 4 ☐
Opalescent 2 ☐ Hemorrágic 5 ☐
Tèrbol 3 ☐

50. LCR (2) pressió…….. ☐☐

51. LCR (2) cèl·lules……..…… ☐☐☐☐☐

52. LCR (2) fórmula (%segmentats)…… ☐☐

53. Hipoglicorràquia (2)……..…… ☐

No 1 ☐ si 2 ☐

54. LCR (2) proteïnes……..…… ☐

<1g 1 ☐ 5-10g 3 ☐
1-5g 2 ☐ >10g 4 ☐

55. LCR (2) gram…….. ☐

Negatiu…… 1 ☐
Positiu…….. 2 ☐
Errada interpretació…… 3 ☐

56. LCR (2) cultiu……..…… ☐☐

57. LCR(3) dia……... ☐☐

58. LCR (3) aspecte……..… ☐

Clar	1 ☐	Purulent	4 ☐
Opalescent	2 ☐	Hemorràgic	5 ☐
Tèrbol	3 ☐		

59. LCR (3) presió……..…. ☐☐

60. LCR (3) cèl·lules…… ☐☐☐☐☐

ANALÍTICA GENERAL

61. Leucòcits……. ☐

<1.000	1 ☐	10.000-15.000	4 ☐
1.000-5.000	2 ☐	>15.000	5 ☐
5.000-10.000	3 ☐		

62. Hemoglobina…… ☐☐

63. Plaquetes…….. ☐

<100.000	1 ☐
100.000-300.000	2 ☐
>300.000	3 ☐

64. Quick……. ☐

>1’2 1 ☐ <1’2 2 ☐

65. Natremia…… ☐

Hiponatrèmia	1 ☐
Normal	2 ☐
Hipernatrèmia	3 ☐

66. Kalièmia…… ☐

Hipokalièmia	1 ☐
Normal	2 ☐
Hiperkalièmia	3 ☐

RADIOLOGIA

67. Tac cranial (abans tt)……..….. ☐

Normal	1 ☐	Infart	5 ☐
Edema cerebral	2 ☐	Hemorràgia	6 ☐
Cerebritis-abscés	3 ☐	Patología antiga	7 ☐
Hidrocefàlia	4 ☐		

68. Tac cranial després de tt (dia)…… ☐☐

69. Tac cranial evolució…….. ☐

Normal	1 ☐	Infart	5 ☐
Edema cerebral	2 ☐	Hemorràgia	6 ☐
Cerebritis-abscés	3 ☐	Patología antiga	7 ☐
Hidrocefàlia	4 ☐		

TRACTAMENT

70-a antibiótic inicial…… ☐☐

70. Antibiótic……. ☐☐

Dosi……..…

Antibiograma……..

……

71. Durada (díes)…… ☐☐

72. Tractament corticoides (abans o amb) ……. ☐

No 1 ☐ si 2 ☐ dxm+manitol 3 ☐

Dosis/durada……..

73. Tractament anticomicial..... ☐

No 1 ☐ si 2 ☐

Dosi/durada…….…..

74. Profilaxi anticomicial…….…. ☐

No 1 ☐ si 2 ☐

Dosi/durada……..

75. Ingrés en UCI…….. ☐

No 1 ☐ si 2 ☐

75bisVentilació mecànica…… ☐

No 1 ☐ si 2 ☐

EVOLUCIÓ I COMPLICACIONS

.....

.....

.....

.....

.....

76. Millora consciència (dia)…….. ☐☐

77. Descens temperatura <38º (dia)…… ☐☐

78. Reaparició febre >38º…… ☐

No 1 ☐ si 2 ☐

79. Artritis……..… ☐

No 1 ☐ si 2 ☐

80. Pericarditis……..….. ☐

No 1 ☐ si 2 ☐

81. Miocarditis-insuf.cardíaca……..…. ☐

No 1 ☐ si 2 ☐

82. Complicacions broncopulmonars……. ☐

No 1 ☐ si 2 ☐

83. Insuficiencia renal (Creat>150)…….…. ☐

No 1 ☐ si 2 ☐

84. Deteriorament funció hepàtica (↑2v FA ò ALT/AST)…… ☐

No 1 ☐ si 2 ☐

85. CID…….. ☐

No 1 ☐ si 2 ☐

86. SIHAD……..…. ☐

No 1 ☐ si 2 ☐

87. Herpes……..… ☐

No 1 ☐ si 2 ☐

88. Gastrointestinals……..…….. ☐

No 1 ☐ si 2 ☐

89. Infecció urinària nosocomial……..…..... ☐

No 1 ☐ si 2 ☐

90. Flebitis x catèter……..…. ☐

No 1 ☐ si 2 ☐

91. Teixits tous-osteoarticular……..….. ☐

No 1 ☐ si 2 ☐

92. Díes totals d' ingrés (des de mng fins alta)……... ☐☐

93. Control CCEE. (dies fins últim control)……. ☐☐☐

94. Seqüeles……. ☐

No	1 ☐	Vies llargues	6 ☐
Necrosi cutània	2 ☐	Trastorn carácter	7 ☐
Epilepsia	3 ☐	Hidrocefàlia-shunt	7 ☐
Parells cranials	4 ☐	Combinació	7 ☐
Sordesa	5 ☐		

95. Recaiguda……. ☐

No 1 ☐ si 2 ☐

96. Mortalitat2 ……..…. ☐

No 1 ☐ si 2 ☐

97. Mortalitat…… ☐

No	1☐		
Causa neurol. Precos	2 ☐	Causa sepsis precos	4 ☐
Causa neurol. Tardia	3 ☐	Causa no neur. tardia	5 ☐

COMENTARIS I RESUM FINAL

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Annexe II

Standardized protocol gathering data of shunt infections in the Infectious Diseases Department, Hospital Universitari de Bellvitge, Barcelona

CRD Infección de Shunt

Número de episodio	
Iniciales del episodio	
NHC	
Edad (años)	
Sexo	1. Hombre 2. Mujer
Año de infección	
Estancia hospitalaria (días)	
Enfermedad de base neuroquirúrgica	1. HSA 2. Hemorragia intracerebral 3. Tumor cerebral 4. MAV 5. Pseudotumor cerebrii 6. Quiste aracnoideo 7. Otros 8. Desconocido
Comorbilidad	
Tipo de shunt	1. VP 2. VA 3. LP
Razón para la implantación de shunt	1.H. comunicante 2. H. obstructiva 3. Fístula LCR 4. Otros 5. Desconocida
Mecanismo de adquisición de la infección	1. Intraoperatorio 2. Por contigüidad a. Herida b. Perforación intestinal c. Sinusitis d. Meningitis e. Otro 3. Hematógeno
CLÍNICA	
Tª >= 37.5ºC	1. Si 2. No 3. Desconocido
Cefalea	1. Sí 2. No 3. Desconocido

Vómitos	1. Sí 2. No 3. Desconocido
Rigidez nucal	1. Sí 2. No 3. Desconocido
Alteración del NC	1. Alerta 2. Obnubilación 3. Coma
Crisis comicial	1. Sí 2. No 3. Desconocido
Dolor abdominal	1. Sí 2. No 3. Desconocido
Signos locales de infección	1. Eritema 2. Dolor local 3. Edema 4. Exudado purulento por herida 5. No signos locales
Fecha de dx de infección	
Tº entre la implantación/manipulación del shunt y el inicio de la clínica (días)	1. <1 mes 2. 1-12 meses 3. >12 meses
Tº entre el inicio de los síntomas y el dx (días)	
Tiempo de retraso dx (Tº entre 1er cultivo y dx de shunt) (días)	
LABORATORIO/DIAGNÓSTICO	
Signos radiológicos de malfunción	
Disfunción del shunt (NCR)	
Leucocitosis valor absoluto (según límite laboratorio)	1. + 2. – 3. No realizados
Hemocultivos	1. + 2. – 3. No realizados
Células LCR	
% PMN	
Proteinas LCR	
Gram LCR	1. + 2. – 3. No realizado

Cultivo LCR1 (al dx)	1. + 2. – 3. No realizado
OrigenLCR1	1. Reservorio Valvular 2. Lumbar 3. Ventricular
Cultivo LCR2 (al dx)	1. + 2. – 3. No realizado
OrigenLCR2	1. Reservorio Valvular 2. Lumbar 3. Ventricular
Etiología 1	
Etiología 2	
Polimicrobiano	1. Sí 2. No
Cultivo de catéter	1.+ 2. – 3. No realizado
FFQ/Absceso cutáneo	1. + 2. – 3. No realizado
TRATAMIENTO ATB	
ATB previo al dx	1. Sí 2. No 3. Desconocido
Tº entre dx e inicio de ATB	
Tratamiento ATB empírico	
Tto antibiótico empírico correcto	1. Sí 2. No
Tratamiento ATB definitivo	
Días de tto antibiótico	
Tratamiento IV/IT	
Días de tto IV/IT	
Motivo de tto IV/IT	
Dosis de tto ATB	
Profilaxis qx (última IQ)	
1ª ESTRATEGIA DE TRATAMIENTO	
1. No cirugía 2. Retirada parcial 3. Retirada completa 4. Cirugía en 1 tiempo 5. Cirugía en 2 tiempos sin DVE	

6. Cirugía en 2 tiempos con DVE	
Exteriorización previa al tto definitivo	1. Sí 2. No
DVE/DLE transitorio previa a la implantación definitiva del shunt	1. Si 2. No
Días de tto qx definitivo	
Omaya	1. Sí 2. No
Tº entre dx y 1ª IQ	
Tº entre dx y 2ª IQ	
Fracaso 1ª estrategia (situación que obliga a cambiar la estrategia inicial)	1. Sí 2. No
2ª ESTRATEGIA DE TRATAMIENTO	
1. No cirugía 2. Retirada parcial 3. Retirada completa 4. Cirugía en 1 tiempo 5. Cirugía en 2 tiempos sin DVE 6. Cirugía en 2 tiempos con DVE	
…	
PRONÓSTICO	
Curación (no evidencia de reinfección por el mismo mo durante el segumiento)	1. Sí 2. No
Recaída (evidencia de reinfección por el mismo mo durante el segumiento)	
Muerte	1. Si 2. No
Días de seguimiento	
Superinfección del DVE/DEL transitorio	1.Sí 2. No
Complicaciones	