PANDRUG RESISTANT *ANICEBACTER BAUMANII* VENTRIKULITIS: FIRST EXPERIENCE OF INTRATECHAL COLISTIN TREATMENT IN SOETOMO HOSPITAL

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INTRODUCTION

Healthcare-associated ventriculitis and meningitis (HAVM) is not an uncommon problem in clinical practice, especially considering the rising rates of neurosurgeries and neurosurgical device surgeries. Compared with community-acquired meningitis, HAVM is different in clinical presentation and pathogens.[1] HAVM significantly impairs patient outcome, association with mortality and morbidity. Post-neurosurgical meningitis increases mortality rate approximately 3 times compared to non-meningitis neurosurgical patient (13.7% vs 4.7%).[2] More over, post-neurosurgical meningitis may lead to prolonged hospital stay, repeat surgery, and increased hospital costs.[3] In clean neurosurgery, the rate of postoperative bacterial meningitis is low (1–2%). The use of devices for therapeutic drainage of cerebrospinal fluid (CSF) or for intracranial pressure monitoring, such as external ventricular drains (EVD), external spinal drains (ESD), and shunts, is associated with an increase in the rate of postoperative meningitis of up to 22%.[4]

Staphylococci and resistant-Gram negative baccili are the most common pathogen caused nosocomial meningitis. CSF cultures that grow *Staphylococcus aureus* or aerobic Gram-negative bacilli are indicative of infection.[1] *Acinetobacter baumannii* has emerged as an important multidrug-resistant (MDR) and pandrug-resistant (PDR) healthcare-associated pathogen.[5] *Acinetobacter baumannii* (*A. baumannii*) is a Gram-negative bacillus of the acinetobacter.[6] It is an opportunistic pathogen that can be detected on human skin and in human tracts connected with the outside world. Thus *A. baumannii* easily causes serious infection of critical patients, such as the one with pneumonia, septicemia, meningitis, etc.[7] The patients after craniocerebral operations in neurosurgery have a high risk to suffer from bacterial meningitis caused by *A. baumannii* and get potentially fatal consequences, associated with external ventricular drainage (EVD), cerebrospinal fluid (CSF) leaking, or head trauma.[8]

Outbreaks caused by MDR *A. baumannii* have been reported from many countries, with anecdotal treatment success using aminoglycosides, carbapenems, b-lactamase inhibitors, tigecycline, rifampin and colistin.[9] Patients with central

nervus system (CNS) infection as a result of PDR *A. baumannii* isolates susceptible to colistin may benefit from adjunct intrathecal or intraventricular (IT/IVT) colistin therapy.[10] The premise for such a regimen is that intravenous (IV) colistin may not achieve adequate CNS penetration, IV treatment failures have been reported, and adverse events related to systemic treatment include nephrotoxicity and neurotoxicity.[11] Tigecycline is a potential alternative, yet it is not approved for meningitis treatment, and CNS pharmacokinetics and pharmacodynamics require further investigation.[12] The use of IT/IVT colistin and aminoglycosides has been reported for MDR/PDR *A. baumannii* meningitis with success rates of greater than 80%.[13]

The purpose of this paper is to report a case of intratechal colistin therapy for healthcare associated ventriculitis caused by pandrug-resistant (PDR) *Acinetobacter baumannii*.

CASE REPORT

A, 1 month old boy patient, came to Emergency Department of Dr. Soetomo Hospital referred from Tuban Hospital, on August 16th 2018 with the chief complaint of seizure since 1 day before admission. Seizure was only on right extremity. Before, patient was vomitting 4 times. There was no fever, no diarrhea and no complaint of dyspnea. One day before, at August 15th 2018, patient was brought to pediatrician with chief complain of vomitting, but no seizure. Patient got sympthomatic drug. At home, patient got seizure on right extremity, and then brought to Tuban hospital. There, patient was done head ultrasonography, revealed suspicious of intraventricular hemorrhage. Patient was referred to Sutomo hospital for advanced therapy.

From the history, patient was never got seizure before, and never got head injury. During pregnancy, the mother never had complain of illness, never consumed herbal medicine, and routinely control to obstetrician. The patient was spontaneously delivered at hospital, term, with 3450 grams of birth weight, 51 cm of birth length, and crying soon after birth. The baby got vitamine K injection after birth. The immunization history was only Hepatitis B. The patient was breastfed, since birth until now.

The physical examination revealed a somnolen boy, 1 month old, with a body height of 56 cm and body weight 5.1 kg. Vital signs showed that the respiratory rate was 40 times/minute, the pulse rate was 150 times/minute regularly, the body temperature was 36.7 ℃.

Head and neck examination revealed anemis, no dyspnea, no jaundice nor cyanosis. Large fontanel was convex. The chest was symmetric, there was no retraction, vesicular breath sound was equal on both lungs. Neither rhales nor wheezing was heard. The heart revealed no murmur and no gallop rhythm. The examination of the abdomen showed that the abdomen was flat, no sign of ascites, the bowel sound was normal, the liver and spleen were not palpable. The extremities were well perfused, no leg edema was seen, capillary refill time was under 2 second. The neurological status was GCS E3V5M6, no meningeal sign found, no nuchal rigidity. The pupil were anisokor with diameter for each 3mm

right and 2mm left, light reflex was decreased in right pupil. Physiologic reflex was decreased in right extremities, pathologic reflex was not found.

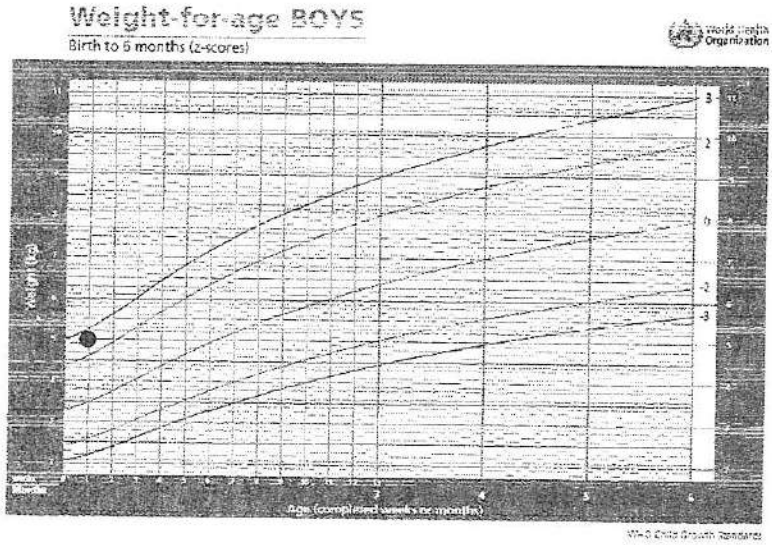

Figure 1. Growth chart showed body weight 5.1 kg, age 1 months. The WAZ was >2

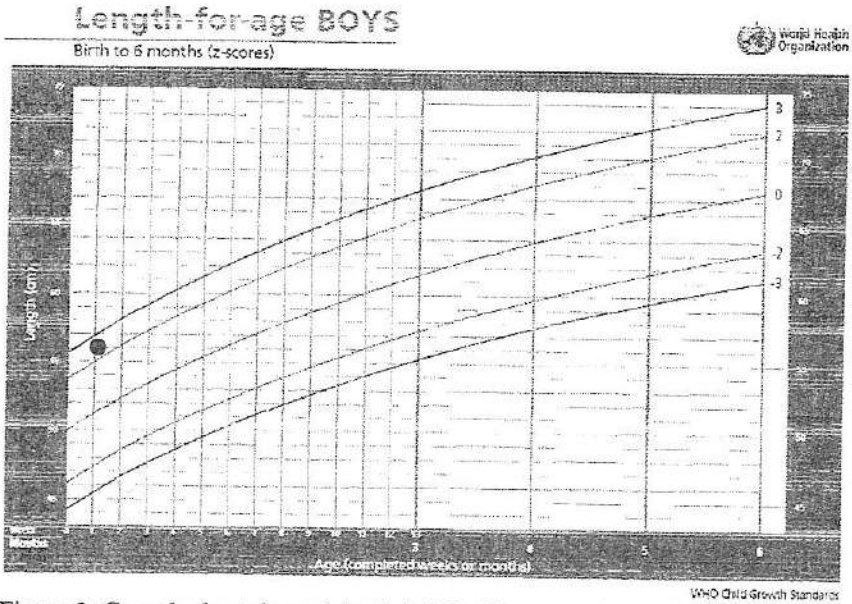

Figure 2. Growth chart showed body height 56 cm, age 1 months. The LAZ was > 2

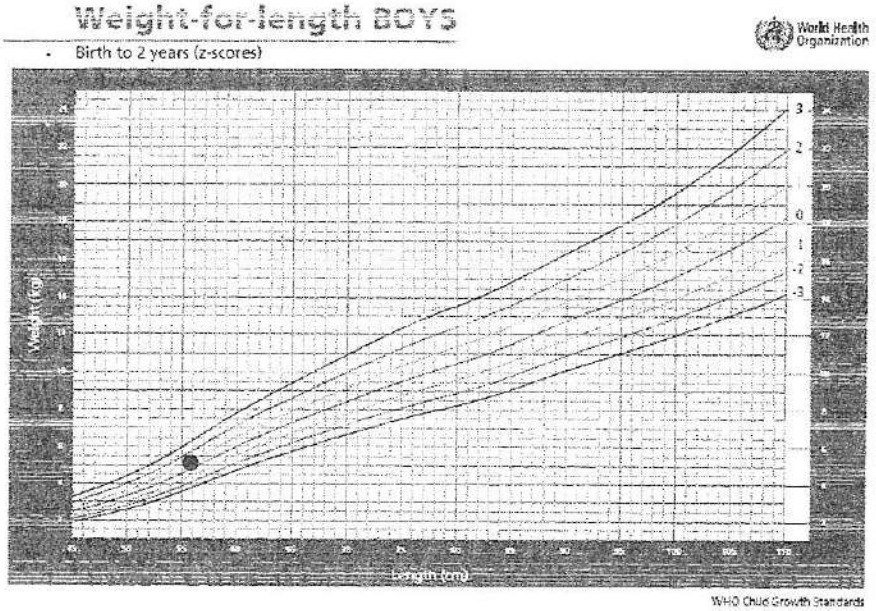

Figure 3. Growth chart showed body weight 5,1 kg, body height 56 cm and the WLZ > 0.

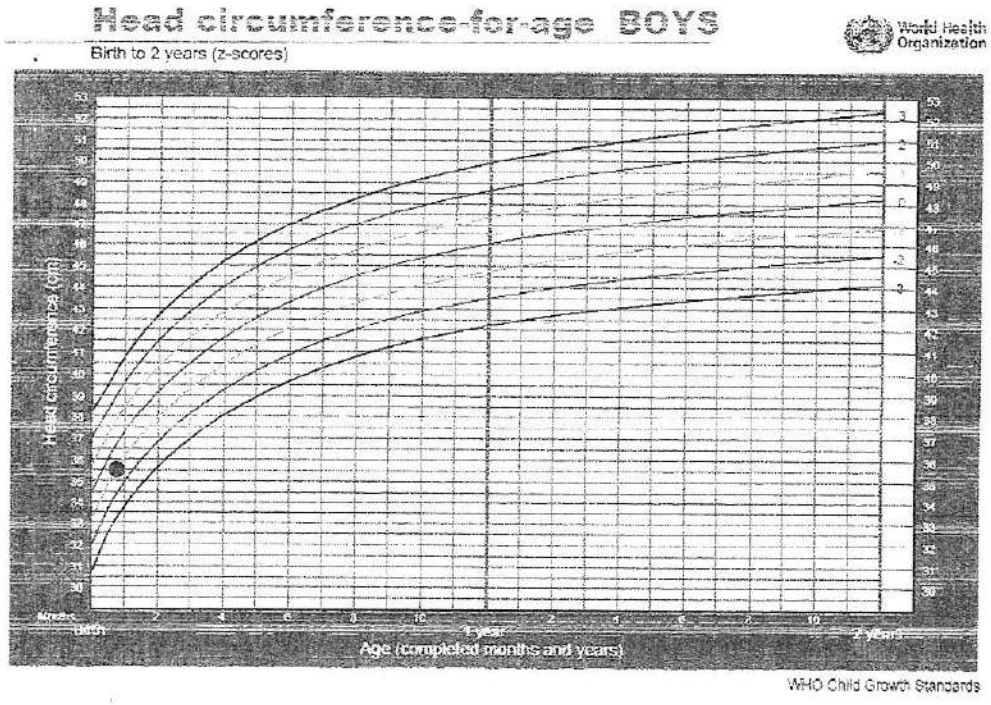

Figure 4. Growth chart showed head circumference 35.5 cm, the HCAZ was < 0.

Initial laboratory finding revealed hemoglobin level of 7 g/dL, leukocytes 12.9 x 10^3/µL, platelets count 278 x 10^3/µL, sodium 134 mmol/l, potassium 4.8 mmol/l, chloride 102 mmol/l, calsium 9.6 mmol/l, CRP 10.4 mg/L. AST 50 u/l, ALT 32 u/l, BUN 4 mg/dL, creatinine serum 0.35 mg/dL, albumin 3.47 g/dl, PPT

10.8 seconds, APTT 28.9 seconds. Chest x-ray revealed no disorder of both lungs and heart. Head CT scan showed intracranial haemorrhage and subdural haemorrhage at left temporoparietooccipital.

From neurosurgery department, patient was assessed as active left temporoparietooccipital subdural haemorrhage and posterior fossa intracranial haemorrhage. Patient was planned for cito operation craniotomy to evacuate the haemorrhage.

Based on the history, clinical manifestation, laboratory finding, and head CT scan, the working diagnosis on admission was acute left temporoparietooccipital subdural haemorrhage and posterior fossa intracranial haemorrhage. Patient was planned for PRC transfusion and evacuation operation after haemoglobin level had increased.

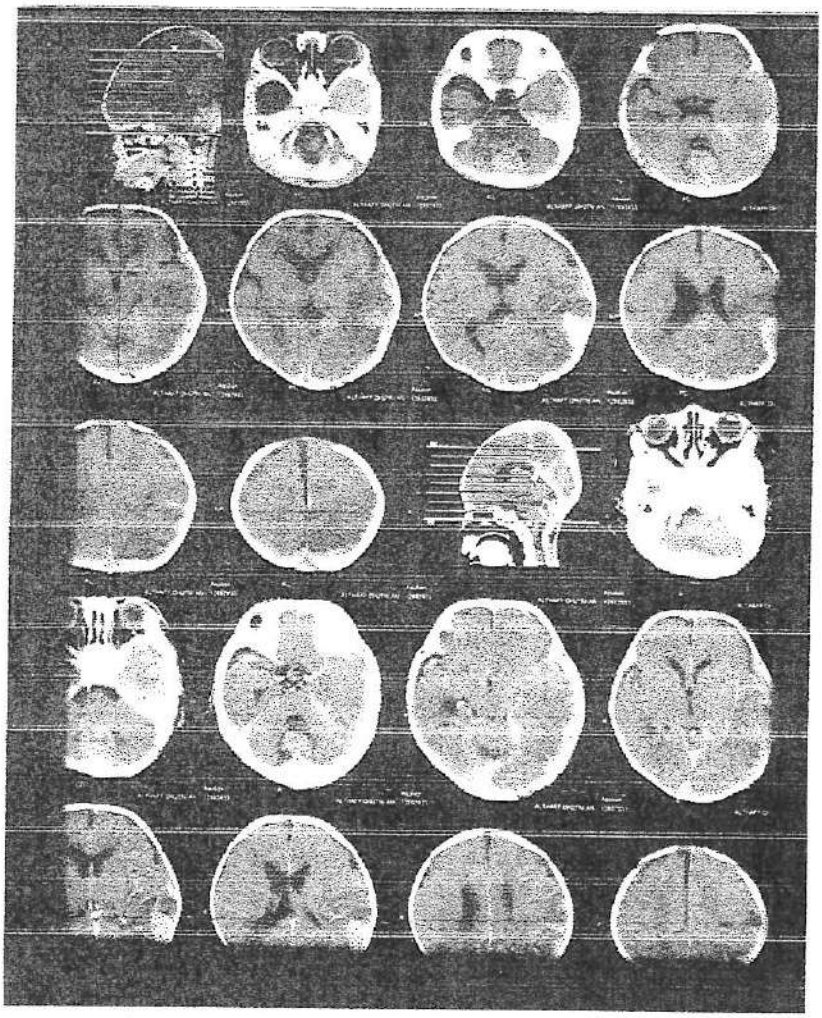

Figure 5. Head CT scan on August 16th 2018 showed ICH and SDH

The first operation to evacuate SDH and ICH was held by neurosurgery department on August 17th 2018. There was 300 ml of blood evacuated. On August 19th 2018, second operation was held for evacuating blood and EVD insertion. Patient showed improvement in general condition after operation. There was no seizure, no fever with stabile vital sign. Cerebral fluid analysis on August 25th 2018 revealed no colour, clear, sedimentation (-), pH 8, MN 93/uL, PMN 214/uL, cell count 317, nonne (+), pandy (+), glucose 44 mg/dL, total protein 147.8 mg/dL. Patient was planned for transfemoral catheter angiography (TFCA) to explore the source of bleeding. On August 29th 2018, TFCA was postponed and the shunt of EVD was released. Patient was planned for discharge from hospital.

On August 30th 2018, patient got fever, vomitting once and general seizure. Laboratory finding revealed hemoglobin 11.1 g/dL, leucocyte 16,940/uL, hematocrite 35.5%, platelet 558,000/uL, CRP level was 17.8 mg/L. Patient was treated with Cefoperazone sulbactam injection, antiseizure drug and thermoregulation.

After 5 days antibiotic, patient stil fever but no seizure. Procalcitonin level was 27.36 ng/L. Antibiotic was continued. Head CT scan was held on September 11th 2018, revealed communicating hydrocephalus; partial absorbed intraventricular haemorrhage at posterior cornu and lateral temporal ventricel; encephalomalaceal cyst at left parietal.

On September 13th 2018, patient was done operation for irrigation endoscopy and insertion of EVD. Cerebral fluid analysis and culture were examined. Cerebral fluid analysis revealed yellowy, clear, sedimentation (-), pH 8, MN 235/uL, PMN 1,194/uL, cell count 1,173, nonne (+), pandy (+), glucose 1 mg/dL, total protein 29.42 mg/dL.

On September 20th 2018, patient stil fever, recurrent seizures were stil present. Cerebral fluid culture revealed *Cronobacter sakazakii complex*, sensitive to Tetracycline. Resistent to Amikacin, Gentamycin, Astreonam, Amoxicillin-clavulanac acid, Ampicilin, Piperacilin, Piperacilin tazobactam, Cephazolin, Ceftazidime, Cefotaxime, Ceftriaxone, Cefoperazone sulbactam, Cloramphenicol, Ciprofloxacin, Levofloxacin, Moxifloxacin, Fosfomycin, Meropenem and

Imipenem. Patient was given antibiotic Tigecyclin intratechal injection 5mg every 12 hours.

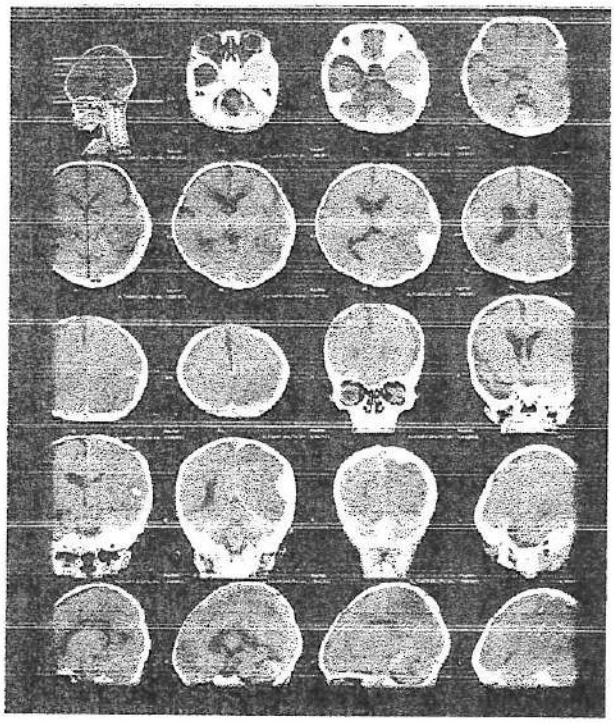

Figure 6. Head CT scan on September 11th 2018 showed communicating hydrocephalus

Evaluation for cerebral fluid culture was done on September 20th 2018, revealed *Acinetobacter baumannii*. No antibiotic was sensitive to the bacteria. Second and third evaluatin cerebral fluid culture was done on September 23th 2018 and September 29th 2018, stil revealed Acinetobacter baumannii with no antibiotic was sensitive. Patient stil got fever and recurrent seizures, with GCS E3V2M4.

On October 5th 2018, patient was stil fever, recurrent seizure with GCS E3V2M4. Antibiotic changed to Colistin intratechal injection 50,000 unit every 8 hours, and planned for operation to change EVD. On October 19th 2018, operation for EVD was held by neurosurgery departement, to remove prior device and change with new device. During Collistin therapy, patient showed clinical improvement. The conciousness was improved, fever was decreased and seizure became rare.

On October 24th 2018, patient with no seizure and no fever. GCS E4V5M6, heart rate 130 bpm, respiratory rate 30 tpm, temperature was 37°C.

Colistin intratechal injection was continued until 21 days. Cerebral fluid culture examined twice at October 16th 2018 (11 days Clolistin) and October 25th 2018 (20 days Colistin), revealed no bacteria or fungal found (sterile).

DISCUSSION

A, 1 month old boy patient, came to Emergency Department of Dr. Soetomo Hospital referred from Tuban Hospital, on August 16th 2018 with the chief complaint of seizure since 1 day before admission. Seizure was only on right extremity. From head ultrasonography and head CT scan, revealed intraventricular and subdural hemorrhage. There were no history of head trauma or sign of another bleeding. The baby had got vitamine K injection after birth. Patient got operation to evacuate SDH and ICH twice and EVD insertion by neurosurgery department one day after admission.

Nontraumatic intracranial hemorrhages (ICHs) are uncommon in children, but often causes death or lifelong disability.[14] In previous reports of pediatric ICH, the etiology of nontraumatic ICH in children were arteriovenous malformations (AVMs), congenital vascular anomaly, hematologic or coagulation disorders and brain tumors.[15] Table 1 shows the etiology of ICH in pediatric is different with in adult. Vascular malformation is the most common etiology of ICH in pediatric patient.[16] Clinical presentation of ICH in children under 6 year were variation, including change of mental status, seizure and vomiting (Table 2).[14] Seizure is the most important symptom in neonates and children with spontaneous ICH. Study by Lauren A Beslow et al, 2013 result that seizures as presenting symptoms occurred in 31 subjects, 12 perinatal (60%) and 19 childhood (36%). Seizure semiology was focal in 10 perinatal and 14 childhood subjects. Five children (9%) and 10 perinatal subjects (50%) presented with status epilepticus.[17]

Upon initial diagnosis of intracerebral hemorrhage on noncontrast CT, workup and treatment should be initiated without delay. The guidelines for the treatment of spontaneous ICH were last updated in 2010, also apply to pediatric patients is shown in Table 3.[16] Conservative management with supportive care may be appropriate for self-limited hemorrhage without progressive mass effect or elevated intracranial pressure (ICP). Several surgical options exist for managing acute ICH requiring intervention. First and foremost are the evaluation and management of "ABCs." Airway, breathing, and circulation. If high intracranial pressure is present, it must be addressed with external ventricular drainage (EVD),

evacuation of the hematoma, and/or decompressive craniectomy with expansile duraplasty depending on the clinical situation and the location of the hemorrhage. If there is suspicion of underlying AVM, limited evacuation of the hematoma is advised only if necessary in cases of mass effect because aggressive evacuation of the hematoma may precipitate AVM re-rupture. The thrombus cap over the rupture site can be tenuous.[16]

Table 1. Most common etiologies of spontaneous intracerebral hemorrhage in adults and children.[16]

Adults	Children
Hypertensive vasculopathy (35%)	Vascular malformations (50%)
Cerebral amyloid angiopathy (20%)	Arteriovenous malformations (39%)
Bleeding diathesis	Cavernous malformations (11%)
Anticoagulation (14%)	Bleeding diathesis (21%)
Systemic disease□related coagulopathies (5%): liver failure, DIC, congenital, thrombocytopenia	Coagulopathies: liver failure, DIC, congenital
Vascular malformations (5%)	Thrombocytopenias: malignant (ALL, AML), congenital (aplastic anemias, bone marrow failure), immune□mediated, autoimmune
Other (21%)	Aneurysm (9%)
Aneurysm	Hemorrhagic primary intracranial tumor (6%)
Hemorrhagic conversion	Other (10%)
Hemorrhagic primary or metastatic intracranial tumor	Hemorrhagic CNS infection
Hemorrhagic CNS infection	Cerebral vasculitis
Drug abuse (cocaine, amphetamines)	Moyamoya disease
Cerebral vasculitis	Illicit drug abuse
Cerebral venous thrombosis	

Incidences are cited in parentheses. Note the differences in incidence of vascular malformations as the etiology (5% versus 50%). ALL: Acute lymphocytic leukemia, AML: Acute myelocytic leukemia, CNS: Central nervous system, DIC: Disseminated intravascular coagulation, ICH: Intracerebral hemorrhage

Table 2. Clinical presentations in children with intracranial haemorrhage[14]

Presenting Sign	Number (%) of Children[a]
Age < 6y (n=34)	
Mental status changes	18 (53)
Convulsions	11 (32)
Vomiting	7 (21)
Respiratory distress	4 (12)
Decreased movement/weakness	4 (12)
Age > 6y (n=51)	
Headache	37 (73)
Mental status changes	29 (57)
Focal neurological deficits	20 (39)
Nausea or vomiting	17 (33)
Convulsions	8 (16)
Miscellaneous[b]	12 (24)

[a] Some children had more than 1 of these signs.

[b] Includes dysphasia, fever, dizziness, stomach, neck or ear pain, bradycardia, respiratory arrest, and abnormal gait.

Table 3. Summary of guidelines for management of spontaneous intracerebral hemorrhage[16]

Emergent Management

Noncontrast head CT to distinguish ICH from ischemic stroke.
Correction of coagulopathy or thrombocytopenia, if present.
For pediatric patients: CTA, CTV, contrast CT, MRA, MRV, and contrast MRI to rule out vascular malformations or hemorrhagic tumors.

Inpatient Management

Admission to neurological ICU and supportive care:
Maintenance of CPP with ICP monitoring, ventricular drainage as necessary, and cautious normalization of hypertension.
Ant i□epileptics for clinically evident or electrographic seizures.
Specialized nursing with neurocritical care protocols in place.
Surgical evacuation for patients with significant mass effect (impending or progressing herniation) and/or elevated ICP.
Staged or same□setting resection of associated hemorrhagic lesion, if identified.

Prevention of Recurrence

Blood pressure control and avoidance of long□term anticoagulation.
For pediatric patients: Regular neuroimaging (postoperative and 1□year DSA, followed by annual CTA or MRA, and DSA every 3 years until age 18) to detect recurrence of vascular malformations.

Rehabilitation

Access to a multidisciplinary, integrated inpatient/outpatient rehabilitation program as early as possible.

Adapted from AHA/ASA 2010 recommendations. Additional recommendations have been added for management of pediatric patients. CPP: Cerebral perfusion pressure, CT: Computed tomography, CTA: CT angiography, CTV: CT venography, DSA: Digital subtraction angiogram, ICP: Intracranial pressure, ICU: Intensive care unit, MRA: MR angiography, MRI: Magnetic resonance imaging, MRV: MR venography

In this case, after 14 days operation, patient got fever, vomiting and general seizure. Laboratory finding revealed leukocytosis, CRP and procalcitonin level was increased, result from CSF analysis was PMN dominantly. Head CT scan evaluation revealed communicating hydrocephalus.

The most common type of healthcare-associated CNS infection is ventriculitis or meningitis, with the major risk factor being recent neurosurgery. Among cranial surgeries, the risk of infection is higher (1-24.4%) when the portion of the skull removed for the surgery is stored for a prolonged period of time before replacement (i.e., craniectomy with delayed cranioplasty), when compared to surgeries in which skull fragments are replaced during the same sterile operation (i.e., craniotomy) (0.3-12%).[18] In terms of timing, two-thirds of healthcare-associated CNS infections are diagnosed within two weeks of surgery, with the remainder being diagnosed months or years later.[19] According to Infectious Diseases Society of America (IDSA) 2017 guideline of HAVM, the typical symptoms and signs in patients with healthcare-associated ventriculitis and meningitis iclude new headache, nausea, lethargy, fever and/or change in mental status, and increased CSF white blood cell count in patients with external ventricular drains could be suggestive of infection. Neuroimaging is recommended in patients with suspected healthcare-associated ventriculitis and meningitis, such as MRI.[1]

Hydrocephalus is one of the rare complications of craniotomy. Wani et al, 2013 reported 3 pediatric patient who developed hydrocephalus after decompressive craniotomy. In patients with head trauma who have undergone decompressive craniectomy, it is hypothesized that a large cranial defect can lead to turbulences in hydrodynamic CSF circulation and cerebral blood perfusion by atmospheric pressure, leading to the development of hydrocephalus.[20] Study by Stephen Honeybul between 2004 and 2010 resulted, of the 159 patients who survived more than 6 months after surgery, 72 patients (45%) developed radiological evidence of ventriculomegaly, and 26 of these 72 patients (36%) developed clinical evidence of hydrocephalus and required a ventriculoperitoneal (VP) shunt. Maximum intracranial pressure prior to decompression ($p=0.005$), subdural hygroma ($p=0.012$), and a lower admission Glasgow Coma Scale score

(p=0.009), were significant risk factors for hydrocephalus after decompressive craniectomy.[21]

In this case, first CSF culture resulted *Cronobacter sakazakii*, sensitive to Tetracyclin. Evaluation culture resulted *Acinetobacter baumanii* with pandrug-resistant (PDR) as the pathogen, three times.

Cronobacter multi-species complex (formerly Enterobacter sakazakii) is a group of Gram-negative bacteria that exists in the environment and which can survive in very dry conditions. *Cronobacter* are regarded as opportunistic pathogens, and have been implicated in newborn and infant infections, causing meningitis, necrotizing enterocolitis and bacteraemia or sepsis, with case fatality rates ranging between 40 and 80 % being reported. Prior to 1985, patients with *Cronobacter* infections were frequently treated with ampicillin, gentamicin and/or chloramphenicol. Today, antimicrobial sensitivity patterns of *Cronobacter* isolates should be determined because multidrug-resistant strains have been reported.[22]

Acinetobacter baumannii, a Gram-negative bacillus that is aerobic, pleomorphic and non-motile, is an opportunistic bacterial pathogen primarily associated with hospital-acquired infections.[23] As a pathogen, *A. baumannii* specifically targets moist tissues such as mucous membranes or areas of the skin that are exposed, either through accident or injury. Once *A. baumannii* is isolated in a hospital environment, this poses a significant risk, particularly in ICU wards where patients are chronically ill. As most of these patients are immunocompromised and spend a prolonged period of time in hospital, they represent a high risk group for *A. baumannii* infection. Patients that acquire artificial devices such as catheters, sutures, ventilators and those who have undergone dialysis or antimicrobial therapy within the past 90 days are also at risk of developing *A. baumannii* infections.[24] The respiratory tract, blood, pleural fluid, urinary tract, surgical wounds, CNS, skin and eyes may be sites for infection or colonization.[23]

While in the 1970s *A. baumannii* is thought to have been sensitive to most antibiotics, today the pathogen appears to exhibit extensive resistance to most first-line antibiotics.[25] *A. baumannii* was associated with a rapid development of

resistance to commonly used antimicrobial agents. The major cause of resistance development is inappropriate use of antibiotics, leading to poor outcomes. Longer periods of hospitalization, longer time on mechanical ventilation, prior use of antibiotics, invasive procedures, severity of illness and underlying diseases are recognized as risk factors of multidrug resistance and and extensively drug-resistant *A. baumannii* infection.[26] The mechanisms of resistance generally fall into 3 categories: (1) antimicrobial-inactivating enzymes, (2) reduced access to bacterial targets, or (3) mutations that change targets or cellular functions.[9] In case of the ability of clinical strains to survive desiccation, antimicrobial therapies and nutrient availability stress, it is hypothesized that is mediated by the microorganism's ability to form biofilms on medically relevant surfaces.[27]

By definition, multidrug-resistant (MDR) is as non-susceptibility to at least one agent in three or more antimicrobial categories. Extensive drug-resistant (XDR) is defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories). And pandrug-resistant (PDR) is defined as non-susceptibility to all agents in all antimicrobial categories (i.e. no agents tested as susceptible for that organism). Thus, a bacterial isolate that is characterized as XDR will also be characterized as MDR. Similarly, a bacterial isolate would have to be XDR in order for it to be further defined as PDR. Figure 7 illustrates that XDR is a subset of MDR, and PDR is a subset of XDR.[28]

Antimicrobial catagories and agents are different for each bacteria. According to current information available from the Clinical Laboratory Standars Institute (CLSI), the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the Food and Drug Administration (FDA) together with the opinion of the Expert Group, the inclusion criteria required that each antimicrobial agent: (i) was currently approved as an antibacterial agent in humans; and (ii) had breakpoints for the organism or organism group. While an antimicrobial agent was excluded from an organism/organism group list if: (i) the organism or the whole organism group was intrinsically resistant to the agent; (ii) the agent achieved therapeutic concentrations only in urine (e.g. nitrofurantoin); or (iii) the organism exhibits widespread acquired resistance to the agent (e.g.

penicillin for S. aureus). For *A. baumannii*, antimicrobial categories and agents used to define MDR, XDR and PDR are showed in Table 4. Aminoglycosides, antipseudomonal carbapenems, antipseudomonal fluoroquinolones, antipseudomonal penicillins with β-lactamase inhibitors, extended-spectrum cephalosporins, folate pathway inhibitors, penicillins with β-lactamase inhibitors, polymyxins, and tetracyclines, are the antimicrobial agents that commonly tested to *Acinetobacter baumannii*.[28]

Table 4. *Acinetobacter* spp; antimicrobial categories and agents used to define MDR, XDR and PDR (worksheet for categorizing isolates)[28]

Antimicrobial category	**Antimicrobial agent**
Aminoglycosides	Gentamicin Tobramycin Amikacin Netilmicin
Antipseudomonal carbapenems	Imipenem Meropenem Doripenem
Antipseudomonal fluoroquinolones	Ciprofloxacin Levofloxacin
Antipseudomonal penicillins + β-lactamase inhibitors	Piperacillin-tazobactam Ticarcillin-clavulanic acid
Extended-spectrum cephalosporins	Cefotaxime Ceftriaxone Ceftazidime Cefepime
Folate pathway inhibitors	Trimethoprim-sulphamethoxazole
Penicillins + β-lactamase inhibitors	Ampicillin-sulbactam
Polymyxins	Colistin Polymyxin B
Tetracyclines	Tetracycline Doxycycline Minocycline

Criteria for defining MDR, XDR and PDR in *Acinetobacter* spp.
MDR: non-susceptible to ≥ 1 agent in ≥ 3 antimicrobial categories.
XDR: non-susceptible to ≥ 1 agent in all but ≤ 2 categories.
PDR: non-susceptible to all antimicrobial agents listed.

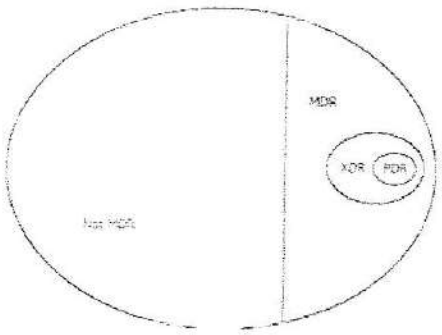

Figure 7. Diagram showing the relationship of MDR, XDR and PDR to each other[28]

In this case, patient got Colistin intratechal therapy 50,000 unit every 8 hours, for 21 days. Evaluation of CSF culture twice, on 11 days and 20 days after initiation of Colistin, revealed sterile.

According to IDSA 2017 guideline of HAVM, meropenem is recommended for treatment of infection caused by Acinetobacter species, but for strains that demonstrate carbapenem resistance, colistimethate sodium or polymyxin B (administered by the intravenous and intraventricular routes) is recommended.[1] Colistin is a 50 year-old antibiotic that is being used increasingly as a 'last-line' therapy to treat infections caused by MDR Gram-negative bacteria, when essentially no other options are available.[29]

Colistin was introduced in clinical use from 1950s, and abrogated in 1980s due to serious renal toxicity and neurovirulence[30] and in 1970s colistin was largely replaced by aminoglycosides. However, in the last 10 – 15 years, colistin has been a limited option and used as 'salvage' therapy for infections caused by multidrug-resistant (MDR) Gram-negative bacteria, in particular P. aeruginosa, Acinetobacter baumannii and Klebsiella pneumoniae.[31] To treat CNS infection, colistin is administered via route intrathecal or intraventricular, when there is concern that intravenous colistin will adequately penetrate into site of infection or when intravenous administration has actually been shown to be ineffective.[29] Nephrotoxicity and neurotoxicity are the most common adverse effects of intravenous administration of colistin. Neurotoxicity is rare, associated with dizziness, weakness, facial and peripheral paresthesia, vertigo, visual disturbances, confusion, ataxia, and neuromuscular blockade, which can lead to

respiratory failure or apnea. The incidence of colistin-associated neurotoxicity reported in earlier literature was ~7%, with paresthesias constituting the main neurotoxic adverse event. Nephrotoxicity is more common and is of most concern to prescribing clinicians. Renal toxicity mainly includes acute tubular necrosis manifested as decreased creatinine clearance and increased serum urea and creatinine levels.[32] A retrospective study done at the Walter Reed Army Medical Center resulted that renal injury caused by colistin is relatively mild and almost always reversible over weeks to months after stopping therapy.[33]

The bactericidal effect of colistin is extremely rapid but there is limited knowledge of the mechanism of antibacterial activity. Since there is only one amino acid difference between colistin and polymyxin B, it is believed that they have the same mechanism of action. Polymyxin B interacts with the LPS of the outer membrane of Gram-negative bacteria and competitively displaces divalent cations (Ca2+ and Mg2+) from the negatively-charged phosphate groups of the lipid A of LPS.[29] The dosage intravenous recommended by the manufacturers in the United Kingdom is 4–6 mg/kg (50,000– 75,000IU/kg) perday, in 3 divided doses for adults and children with body weights of < 60 kg and 80–160 mg (1–2 million IU) every 8 h for those with body weights of > 60 kg. There are few recent reports in the literature about the direct administration of colistin in CSF for the management of infections of the CNS due to MDR Gram-negative bacteria.[32] Systematic review and case series done in Thai Hospital 2009, from 24 cases of MDR and PDR A.baumannii, the clinical and microbiological cure rates were above 80%, and the commonly administered dose, was 40 000–500 000 IU/ day (1 mg of colistin equals 30 000 IU of colistin and 1 mg of colistimethate equals 12 500 IU of colistin), mixed with 0.9% sodium chloride, given once or twice daily through a ventricular catheter or a spinal needle after an equivalent volume of CSF was extracted. For patients with an external ventricular drain, the drainage was interrupted for 2 hours. Duration of therapy was in a range of 2–3 weeks but may have varied depending on clinical response, with sterilization of the CSF expected within 72 hours. The median duration from initiation of therapy to CSF sterilization was 3 days (range 1–23 days).[13]

In this case, patient got operation to change device for EVD besides antibiotic therapy.

External ventricular catheters are used for the monitoring of intracranial pressure or the temporary diversion of cerebrospinal fluid from an obstructed ventricular system, or as part of the treatment approach for infected internal catheters. The rate of infection associated with external catheters is approximately 8%. The risk of infection is reported to be increased with an increased duration of drainage, but the extent of increase per unit of time is uncertain. Other risk factors for infection are the routine sampling of cerebrospinal fluid, leakage of cerebrospinal fluid at the site, blockage of the drain, and intraventricular hemorrhage.[34] Catheter infection probably results from bacterial colonization of the catheter near the insertion site, and migration of pathogens along the device tract. Therefore, in case of infection catheter removal has been recommended. In a decision analysis model based on literature review, removal of all the components of the device and placement of a temporary EVD, combined with antimicrobial therapy, was the best treatment strategy in general, with an 85% cure rate.[35]

Bacterial colonization on the surface of the device may formed by biofilms. A biofilm is an assemblage of microbial cells that is irreversibly associated (not removed by gentle rinsing) with a surface and enclosed in a matrix of primarily polysaccharide material. Noncellular materials such as mineral crystals, corrosion particles, clay or silt particles, or blood components, depending on the environment in which the biofilm has developed, may also be found in the biofilm matrix. Biofilm-associated organisms also differ from their planktonic (freely suspended) counterparts with respect to the genes that are transcribed. Biofilms may form on a wide variety of surfaces, including living tissues, indwelling medical devices, industrial or potable water system piping, or natural aquatic systems. Figure 8 shows scanning electron micrograph of a staphylococcal biofilm on the inner surface of an indwelling medical device.[36] A spectrum of indwelling medical devices or other devices used in the health-care environment have been shown to harbor biofilms, resulting in measurable rates of device-associated infections.[37] Table 5 provides a listing of microorganisms commonly associated with biofilms on indwelling medical devices.[36] Characteristics of

biofilms that can be important in infectious disease processes include a) detachment of cells or biofilm aggregates may result in bloodstream or urinary tract infections or in the production of emboli, b) cells may exchange resistance plasmids within biofilms, c) cells in biofilms have dramatically reduced susceptibility to antimicrobial agents, d) biofilm-associated Gram-negative bacteria may produce endotoxins, and e) biofilms are resistant to host immune system clearance.

Table 5. Microorganisms commonly associated with biofilms on indwelling medical devices[36]

Microorganism	Has been isolated from biofilms on
Candida albicans	Artifical voice prosthesis Central venous catheter Intrauterine device
Coagulase-negative *staphylococci*	Artificial hip prosthesis Artificial voice prosthesis Central venous catheter Intrauterine device Prosthetic heart valve Urinary catheter
Enterococcus spp	Artificial hip prosthesis Central venous catheter Intrauterine device Prosthetic heart valve Urinary catheter
Klebsiella pneumoniae	Central venous catheter Urinary catheter
Pseudomonas aeruginosa	Artificial hip prosthesis Central venous catheter Urinary catheter
Staphylococcus aureus	Artificial hip prosthesis Central venous catheter Intrauterine device Prosthetic heart valve

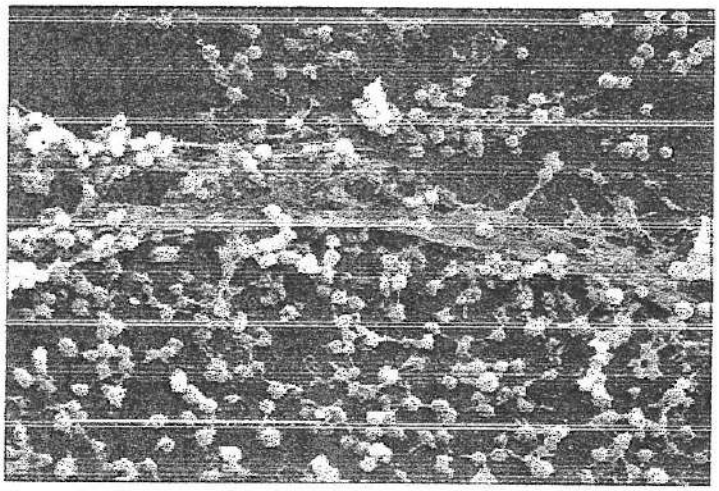

Figure 8. Scanning electron micrograph of a staphylococcal biofilm on the inner surface of an indwelling medical device.[36]

SUMMARY

A case of healthcare-associated ventriculitis caused by pandrug-resistant *Acinetobacter baumannii* in 1 month old boy have been reported. Signs and symptoms of ventriculitis emerge approximately 2 weeks after neurosurgery operation and insertion of external ventricular drainage (EVD), include new fever, vomiting and general seizure. Laboratory finding revealed leukocytosis, increase of CRP and procalcitonin level, CSF analysis was PMN dominantly, and cerebrospinal fluid culture revealed pandrug-resistant *Acinetobacter baumannii*. Colistin intratechal therapy was given to the patient for 21 days combine with removal of EVD catheter, in association of catheter infection by bacterial colonization on the device. Evaluation CSF culture were sterile in twice examination, in 11 days and 20 days after initiation of intratechal colistin.

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Certificate of Attendance

This is to certify that

Dominicus Husada

Attended the sessions listed in the appendix below during the:

37th Annual Meeting of the
European Society for Paediatric Infectious Diseases

Held in:

Ljubljana, Slovenia | May 6 – 11, 2019.

Marko Pokorn **Goran Tešović**

Chairs, ESPID 2019 Meeting

Session Attendance

Title	Date	Time
INDUSTRY SYMPOSIUM 3	06/05/2019	14:45 - 16:15
INDUSTRY SYMPOSIUM 4	06/05/2019	16:45 - 18:15
INDUSTRY SYMPOSIUM 5	06/05/2019	18:30 - 20:00
INDUSTRY SYMPOSIUM 6	07/05/2019	08:00 - 09:15
INDUSTRY SYMPOSIUM 7	07/05/2019	09:30 - 11:00
INDUSTRY SYMPOSIUM 8	07/05/2019	11:30 - 13:00
INDUSTRY SYMPOSIUM 9	07/05/2019	13:45 - 15:15
PIDS/ESPID JOINT PLENARY SYMPOSIUM - THE FUTURE OF VACCINES (IS NOW)	07/05/2019	15:30 - 17:00
ESPID PLENARY 2 - OPENING SYMPOSIUM - ANTIBIOTIC USE ACROSS EUROPE – DIFFERENCES AND CHALLENGES	07/05/2019	17:30 - 19:30
ADVAC SESSION	07/05/2019	20:00 - 21:30
MEET THE EXPERT 5 - PREVENTION OF VERTICAL TRANSMISSION OF HIV	08/05/2019	07:00 - 07:50
PLENARY SYMPOSIUM 3 - ONE HEALTH – THE HUMAN – ANIMAL INTERFACE	08/05/2019	08:00 - 09:30
ORAL PRESENTATION SESSION 3 - NEONATAL INFECTIONS	08/05/2019	10:00 - 11:00
ESPID SYMPOSIUM 1 - PAEDIATRIC SEPSIS	08/05/2019	13:40 - 15:10
ESPID SYMPOSIUM 2 - VACCINE CHALLENGES	08/05/2019	13:40 - 15:10
ESPID SYMPOSIUM 3- PERINATAL INFECTIONS - THE MOTHER - INFANT PAIR	08/05/2019	13:40 - 15:10
ESPID SYMPOSIUM 8 - CONGENITAL CMV INFECTION	08/05/2019	15:40 - 17:10

ESPID 2019 Travel Award Notification

Yahoo Inbox

- **DiyanaYosifova** <dyosifova@kenes.com>

To:dominicushusada@yahoo.com

1 Mar at 6:59 pm

37th Annual Meeting of theEuropean Society for Paediatric Infectious Diseases

Ljubljana, Slovenia | May 6 – 11, 2019

Dear Dr. DominicusHusada,

We are pleased to inform you that your application was accepted to receive the **ESPID Annual Meeting Travel Award.** Accepted applicants receive benefits including support for economy class air and/or train travel to Ljubljana, Slovenia, accommodation for up to 5 nights at the Park Hotel, and free registration for the Meeting.

Please note: Applicants are required to register, book their accommodation, and contact the travel agency by March 12, 2019. Applicants who fail to do so will be removed from the award scheme entirely. It is essential that you follow the procedures set out below. Bookings done independently WILL NOT BE REIMBURSED.

REGISTRATION & HOTEL ACCOMMODATION

Please click here to register and book your accommodation.

TRAVEL SUPPORT

In order to receive support for your travel to the Meeting, you will need to make all travel arrangements to the Meeting via our officially appointed travel agent, Ophir Tours. **Travel bookings made on your own will not be reimbursed.** Please note that the conditions of the funding given to ESPID for the award scheme prevent us from reimbursing any expenses and payments you make yourself.

Please contact the official travel agent at: espid-grant@cwt.co.il with your required arrival and departure dates and the airport and/or railway station from which you will be travelling to the Meeting. Please send as well: names as in passport, gender, date of birth and mobile number. Please note that the offered travel options which meet your allocated travel amount may be direct or indirect flights and, for train travel, may be at off peak times.

- If you are travelling by air, please note that travel between your home and your local airport, and between the Ljubljana airport and the venue cannot be funded as part of the travel support. You will need to cover these costs yourself.
- Please note that once a flight/train ticket is booked, changes cannot be made to the booking.

ATTENDANCE DURING THE MEETING

ESPID requires recipients of the travel award to attend sessions throughout the entire Meeting. Attendance is logged by scanning the personal name badge on entry to each session hall. Any award recipients whose logged attendance falls below 80% of timetabled periods during the main Meeting (Tuesday pm to Friday am inclusive) will be permanently excluded from applying for ESPID travel awards in the future. Accordingly, you should not accept this award unless you intend to be present throughout the Meeting. If you accept, **it is critical that you log your presence at every session you attend.**

We look forward to seeing you in Ljubljana!

Best wishesESPID 2019 Meeting Organiser