Journal of the Medical Research Institute

JMRI, 2022; Vol. 43 No. 2: (9-12)

Journal of the Medical Research Institute

EFFECTIVE TREATMENT OF MENINGITIS CAUSED BY MULTIPLE ORGANISMS INCLUDING MDR E. COLI, MDR KLEBSIELLA PNEUMONIAE AND MRSA: A CASE REPORT

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ABSTRACT:
Following neurosurgical intervention, meningitis caused by resistant microorganisms progresses with substantial morbidity and mortality. Treatment is challenging because there are few antibiotics that can cross into the cerebrospinal fluid and act on these organisms. It is advised to administer intraventricular antibiotics in the treatment of meningitis. Hereby, we are presenting a 2-month-old infant presented to the hospital with fever, hypoactivity and decrease in oral intake. This infant had inserted a shunt a month before this presentation. Upon full examination, the infant was diagnosed to suffer from a meningitis caused by multiple organisms including MRSA, MDR E. coli and MDR Klebsiella pneumoniae. The infection was successfully managed with a combination therapy which included, vancomycin, meropenem, amikacin and later on colistin through different routes of administration.

Keywords: Meningitis, MDR Infections, Successful Treatment

1. INTRODUCTION

The World Health Organization has identified antimicrobial resistance as one of the major threats to world health [1]. Methicillin resistance Staphylococcus aureus (MRSA) is one of the major bacterial isolates that can cause a wide range of diseases ranging from skin and soft tissue infections to lethal bacteraemia. Several cases of acute bacterial meningitis are caused by MRSA [2]. Although some cases of MRSA meningitis are treated with intrathecal or intravenous teicoplanin and linezolid [3, 4], vancomycin with or without rifampin is typically the drug of choice. Vancomycin, however, has a slow action and it is bacteriostatic, and MRSA isolates are now exhibiting rising MICs against it. In the lack of inflamed meninges or when administered with dexamethasone, vancomycin has poor CSF penetration [5, 6]. The management of MRSA meningitis in individuals who experience a reaction to vancomycin continues to be clinically difficult.

The two most significant Enterobacterales that frequently cause infections are E. coli and Klebsiella spp. [7]. Carbapenemase-producing Enterobacterales (CPE), which are multi-drug resistant (MDR) bacteria, have a rapid global spread [1, 8]. They have recently emerged as a significant source of infections of the central nervous system and pose a serious danger to public health. Since Carbapenemase can hydrolyze all carbapenems, cephalosporins, and beta-lactams, such organisms pose a therapeutic challenge [9].

A very few drugs, such as Tigecycline and Colistin can effectively treat MDR E. coli and Klebsiella pneumoniae. It is always a challenge for most medications to reach the minimal inhibitory concentration (MIC) in the cerebrospinal fluid (CSF) due to the poor penetration of the blood brain barrier (BBB). There are a lot of clinical studies which have attempted to manage central nervous system bacterial infections using intraventricular (IVT) injections to overcome this problem [10, 11].

To-date, there is no a well-established treatment regimen for bacterial CNS infections caused by a mixture of MDR.

Case presentation

A 2-month-old infant presented to the hospital with fever, hypoactivity and decrease in oral intake. Shunt insertion was done one month before this admission. On admission, the infant was mottled, and presented with decreased pulsation. Her vital signs were: Heart rate 170 beats per minute, Blood pressure 60/70 mmHg, temperature 38oC, Respiratory rate 40 breath per minute, Capillary filling time was 4 seconds, and oxygen saturation was 100% on room air. There were two visible ulcers draining pus on the right side of the neck and the abdomen. The shunt was seen through these ulcers. On admission full lab and CFS analysis (tables, 1, 2) in addition to swabs from the ulcers and CSF sample were withdrawn. The infant afterwards started empiric treatment with Vancomycin (15mg/kg/dose) every 6 hours accompanied with meropenem (40mg /kg/ 8hours) on extended

Received: 3-12-2021 Accepted: 18-1-2022
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infusion over 4hours, waiting for the culture results

After culture results IV Amikacin (30mg/kg/day) was added In the Microbiology Lab, a portion of the CSF was inoculated into a Bact-Alert Blood culture bottle (bioMérieux, France). Another part of the CSF was cultured on Chocolate agar, Blood agar, Sabouraud Dextrose agar and MacConkey's agar, (Condalab, Madrid, Spain) and incubated at 37 oC for 48 hours. A Gram-stained smear was examined using a light microscope. Gram stained have revealed a very high count of neutrophils and a mixture of gran-negative-bacilli and gram-positive cocci.

After 24 hours, the CSF culture revealed a really surprising growth. There was a mixture of Klebsiella pneumoniae subsp. pneumoniae, E. coli and S. aureus. The bacterial isolates were primarily identified by colony morphology accompanied by Gram-staining. Then they were furtherly identified and antibiotic susceptibility (AST) was done using Vitek 2 Compact system (bioMérieux, France) according to the manufacturer's instructions.

Upon analysing the AST results, it was interpreted that the infant is suffering from a meningitis caused by MRSA, MDR Klebsiella pneumoniae and MDR E. coli. Both Klebsiella and E coli were found to be resistant to carbapenems. The MIC of the AST are showed in table 3. Cultures from both wound ulcers revealed growth of the same organisms.

Depending on the culture results and aiming for a successful treatment regimen, the shunt was removed then an extra-ventricular drain was inserted. Intraventricular Amikacin (30 mg) and Vancomycin (20 mg) were started.The infant become off fever 48 hours after admission with improvement of oral intake and inotropes were stopped after 4 days.

A new CSF sample was withdrawn on the 11th day of admission. It revealed no growth of MRSA but the Klebsiella pneumoniae and E. coli isolates became resistant to Amikacin and persisted. Thereby, both IV and intraventricular Amikacin were stopped and they were substituted by IV Colistin at a dose (25000 IU/kg/dose /8 hour) and intraventricular Colistin at a dose of 150000 IU every 24 hours was added.

On the 18th day of admission, all culture results revealed no growth. This was followed by another two confirmatory cultures showing no bacterial growth which indicated the successful treatment of this rarely reported case. The infant condition became generally very healthy.

Discussion and Conclusion:

The frequent neurosurgery procedures, especially in paediatrics, have raised the prevalence of the health-care associated meningitis and ventriculitis. Bacterial CNS infection has significant morbidity and mortality [11]. In USA, Turkey, and China, meningitis induced by MDR bacteria post-neurosurgery has been documented [12, 13].

It is still an obstacle to treat MDR infections especially when there is a challenge to cross the BBB. Recent research indicates that antimicrobial combination therapy may be more effective than monotherapy, and it is advised to use meropenem as the main ingredient in combination regimens whenever feasible [14].

In this case, the bacterial isolates causing the infection included MRSA, carbapenem resistant E coli and carbapenem resistant Klebsiella pneumoniae. It was clear that these isolates have gained access from the ulcers that were seen on the infant right side of the neck and on the abdomen. This infant was definitely colonised with MRSA in the inguinal and axillary areas. By screening its stool for CPE, it was found that the normal flora contained the same resistant Enterobacterales strains. These resistant strains are always found in patients that are frequently admitted to hospitals, stay for prolonged intervals and exposed to multiple broad-spectrum antibiotics. Consequently, the bad hygienic practice and the inattentive care that was followed with the infant after installation of the shunt had led to the ulcer development through which the bacterial strains found their way to the CSF.

Relying on the past MRSA screens and the result of the Gram stain, vancomycin was added combined with double dose of meropenem on extended infusion to cover MRSA and the gram-negative bacilli that were reported. This regimen was then modified and IV Amikacin was added on top of these two antibiotics.

After final culture results and due to the high resistance level of the detected microorganisms, the neurosurgeons removed the shunt and inserted an extra-ventricular drain. Intraventricular Amikacin (30 mg) and Vancomycin (20 mg) was initiated.

The general condition of the infant was better. MRSA was eradicated but unfortunately the cultures were still positive for the gram-negative organisms. Moreover, the Klebsiella developed resistance to Amikacin (MIC $\geq$ 32 mg/l). Therefore, the IV and the intraventricular Amikacin were stopped and Colistin was added through both administration routes. After nearly 7 days from Colistin administration, the CSF of the infant showed no bacterial growth which indicated a successful treatment regimen.

Due to inadequate blood-brain barrier penetration, which results in low-dose drug concentration in the CSF and therapy failure, the use of parental colistin alone in the treatment of meningitis is discouraged. Even when it is given in the right doses, there is an increased chance of nephrotoxicity and, less frequently, neurotoxicity [15, 16]. In instances where systemic antibiotic therapy is ineffective for the treatment of ventriculitis and meningitis associated with healthcare, the Infectious Disease Society of America advises using intraventricular therapy [17].

Different treatment plans, such as intravenous ceftazidime/avibactam and intraventricular gentamicin, parental tigecycline and amikacin with intraventricular amikacin, and meropenem and intraventricular colistin, were used in various other trials [12, 13, 18-21].

In conclusion, very good care should be given and strict infection control practices should be applied during and post neurosurgeries especially to those patients who insert a shunt. MRSA, ESBL and CPE screens prior to neurosurgeries help to guide the prophylactic antibiotics perioperative and the empiric treatment as well in case the patient developed an infection. Combined antimicrobial agents through different administration routes is always the best was to overcome resistant pathogens.

Table 1: CSF analyses results

Day	Aspect	Glucose (mg/dl) [40.0 - 80.0]	Protein (mg/dl) [15.0 - 45.0]	LDH U/l [0 - 26]	CL Mmol/l [110 - 130]	Neutrophil x10^3/cm	Lymphocytes x10^3/cm
On admission	Turbid	2	175.62	1457.51		600	40
5th day	Highly turbid	5.86	226.37	12040	108.50	24000	1200
11th day	Turbid	4.64	224.05	15097	112.50	84800	800
18th day	Turbid	18.70	183.40	11553	116.70	450	200

Table 2: Laboratory Results (CBC+CRP)

Date	WBC	RBC	HGB	HCT	Neutrophil	Lymph	PLAT	CRP
On admission	8.23	3.4	9	25.8	2.37	3.94	247	84.9
7th day	13.81	4	10.6	31.2	4.99	7.5	201	71.2
14th day	13.15	3.8	10.3	29.5	2.1	9.23	214	67.8

Table 3: AST of the isolates revealed on the first culture withdrawn upon admission

MRSA		**E. coli**		**Klebsiella pneumoniae**	
Cefoxitin Screen		ESBL		ESBL	
Positive		**Positive**		**Positive**	
Clindamycin Inducible resistance		Carbapenemase Phenotype		Carbapenemase Phenotype	
Negative		**Detected**		**Detected**	
Oxacillin MIC ≥ 4	R	Ticarcillin MIC ≥ 128	R	Ticarcillin MIC ≥ 128	R
Benzyl Penicillin MIC ≥ 0.5	R	Piperacillin MIC ≥ 128	R	Piperacillin MIC ≥ 128	R
Gentamicin MIC = 4	S	Piperacillin Tazobactam MIC ≥ 128	R	Piperacillin Tazobactam MIC ≥ 128	R
Ciprofloxacin MIC ≤ 0.5	S	Ceftazidime MIC ≥ 64	R	Ceftazidime MIC ≥ 64	R
Moxifloxacin MIC ≤ 0.25	S	Cefepime MIC ≥ 64	R	Cefepime MIC ≥ 64	R
Erythromycin MIC ≤ 2	S	Aztreonam MIC ≥ 16	R	Aztreonam MIC ≥ 16	R
Clindamycin MIC ≤ 0.25	S	Meropenem MIC ≥ 16	R	Meropenem MIC ≥ 16	R
Vancomycin MIC = 2	S	Tobramycin MIC ≥ 16	R	Tobramycin MIC ≥ 16	R
Teicoplanin MIC ≤ 0.25	S	Amikacin MIC = 16	S	Amikacin MIC = 16	S
Linezolid MIC = 2	S	Gentamicin MIC ≤ 4	S	Gentamicin MIC ≤ 1	S
Tetracycline MIC ≤ 1	S	Ciprofloxacin MIC ≥ 4	R	Ciprofloxacin MIC = 1	R
Tigecycline MIC ≤ 0.12	S	Minocycline MIC = 2	S	Minocycline MIC = 2	S
Rifampin MIC ≤ 0.5	S	Colistin MIC ≤ 0.5	S	Colistin MIC ≤ 0.5	S
Trimethoprim Sulfamethoxazole MIC ≤ 10	S	Trimethoprim Sulfamethoxazole MIC ≥ 320	R	Trimethoprim Sulfamethoxazole MIC = 40	S

Declarations

Ethical Consideration: The report applied the World Medical Association Helsinki Declaration for studies on human participants. Then took the approval of the Ethics Committee of the Medical Research Institute, Alexandria University (IORG#: IORG0008812). Written informed consent was obtained from the patient's guardian for participating in this case report.

Conflict of interests: The authors declare that they have no competing interests

Funding: No fund received

Authors Contributions

Dr Eman Hamza: Study conception and design, data collection and clinical outcome monitoring, final interpretations, and draft manuscript preparation.

Dr Shahinda Rezk: Practical Microbiology and Molecular diagnostics, data collection, and draft manuscript preparation and final revision

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