ORIGINAL ARTICLE

PATTERN OF ORGANISMS CAUSING CENTRAL NERVOUS SYSTEM SHUNT RELATED INFECTIONS AND THEIR ANTIBIOTIC SUSCEPTIBILITY PROFILE IN A TERTIARY CARE SETUP

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ABSTRACT

Background: Central nervous system (CNS) shunt-associated infections pose a significant threat, necessitating an in-depth understanding of the frequency and antimicrobial sensitivity patterns of the implicated pathogens. This research aimed to ascertain the frequency and antimicrobial sensitivity patterns of pathogens isolated from central nervous system shunt associated infections.

Material and Methods: This cross-sectional study was conducted from April to September 2020 at the Neurosurgical department of Combined Military Hospital, Rawalpindi, and the Department of Microbiology, Armed Forces Institute of Pathology. 95 cerebrospinal fluid samples obtained through direct aspiration. The study employed standard microbiological techniques for pathogen isolation, identification, and antimicrobial susceptibility testing following CLSI guidelines 2019.

Results: Pathogens isolated from central nervous system shunt associated infections included *Staphylococcus* spp. (29.47%), *Escherichia coli* (16.84%), *Acinetobacter baumannii* (13.68%), *Klebsiella pneumoniae* (10.53%), *Pseudomonas* spp. (8.42%), *Enterococcus* spp. (7.37%), *Morganella morganii*, *Enterobacter cloacae*, and *Candida* spp. (2.11% each), *Stenotrophomonas maltophila* (1.05%), and mixed infections. Among Gram-negative pathogens, 95% were susceptible to Polymixin B, 93% to Meropenem, and 55% to Cefepime. All Gram-positive organisms were sensitive to Vancomycin and Linezolid (100%).

Conclusion: *Escherichia coli*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* were prevalent Gram-negative rods in infections related to CNS shunts, with *Staphylococcus* spp. following. Gram-negative bacteria exhibited sensitivity to Polymixin B, Meropenem, and Cefepime, while Gram-positive organisms were responsive to Vancomycin and Linezolid. The significant occurrence of Gram-negative rods emphasizes their consideration in empirical antimicrobial therapy recommendations for minimizing death and disability.

Keywords: Shunt-associated infections of central nervous system, Antibiotic sensitivity, Gram Negative Rods, Meropenem

BACKGROUND

CSF shunts are mechanical channels that drain CSF from the ventricles to a distal site for absorption. The aim of shunt is to decrease the raised intracranial pressure and is indicated to alleviate the symptoms of congenital hydrocephalus, brain tumors, intracranial hemorrhage, post traumatic hydrocephalus, myelomeningocele, dandy walker syndrome and Neurocysticercosis to name a few.[1,2] Shunt devices are mainly of two types: internalized shunts and externalized shunts. Internalized shunts are further of many types depending upon the location of drainage of their distal portion, i.e., Ventriculoperitoneal (VP), Ventriculopleural (VPL), Ventriculoatrial (VA), Ventriculosubgaleal (VSG) and Lumbar Peritoneal (LP) types. Externalized devices include temporary external ventricular drains (EVDS) and Ommaya reservoirs for administration of antibiotics and chemotherapeutic agents.[3,4] Ventriculoperitoneal (VP) shunts and External ventricular drains are most commonly used in our setup. The most common causes of improper functioning of shunts are shunt blockade, hemorrhage into brain

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Parenchyma and infections. The clinical manifestations of shunt infections are subtle and can range from few or no symptoms to fever, progressive deterioration of conscious level, new headache, lethargy, nausea, vomiting and seizures. Signs of meningeal irritation are usually lacking. As with any implanted foreign hardware, infection is a major squeal leading to long term Cognitive Impairment, Neurological defects even death. Thus, it is essential to start appropriate therapy for treatment of CSF shunt infections for better patient outcome. The incidence of CNS shunt infections in various studies ranges from 5-15%.[5-7]The common pathogens isolated from CSF shunt infections (SI) include Coagulase negative *Staphylococcus, Staphylococcus aureus,* Gram negative Bacilli like *Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae*, and *Cutibacterium acnes*. Mixed infections i-e two isolates were also accounted for infection in few cases.[8]This study's purpose was to evaluate the range of organisms involved in CNS shunt infections and their antibiotic susceptibility profiles in our setup and thus will help in designing Empirical antimicrobial therapy for future.

MATERIAL AND METHODS

This descriptive, cross-sectional study was conducted for a period of six months, from 1st April 2020 to 31st September 2020 at Department of Microbiology / Armed Forces Institute of Pathology Rawalpindi and Neurosurgical department of Combined Military Hospital Rawalpindi. Non-probability, consecutive sampling was done. By using WHO sample size calculator, taking prevalence 40%[5], confidence interval 95%, margin of error (d) 10%, and response rate 100%, the estimated sample size is n=95. CSF Shunt infection will be defined by presence of bacteria in gram stain and culture of CSF obtained either from shunt, ventricles and CSF shunt hardware i-e shunt tip, shunt valve along with other symptoms and signs (fever, altered sensorium, seizures, nausea and vomiting) and no less than one of the following laboratory parameters. CSF cell count >5 cells/µl, CSF glucose < 2.25 mmol/l. CSF Proteins >45mg/dl, CRP >10mg/l. TLC <4.5 OR >11X10^9/l. The study included all CSF samples that were obtained through lumbar puncture with a CSF shunt in situ, ventricular tap, or direct aspiration from a CSF shunt. No discrimination was made on the basis of age and gender. Excluded from the analysis were repeat cerebrospinal fluid (CSF) samples from the same patient, as well as contaminated specimens exhibiting growth of more than two organisms.

Permission from institutional ethical committee was taken (READ-IRB/20/879) and informed consent was taken from the patient. Age, gender, hospital identity and other particulars were recorded on specially designed Performa. All specimens were inoculated on blood agar, MacConkey's agar, Chocolate agar, Sabouraud's agar and anaerobic media culture plates. Culture plates were incubated at 35ºC (+2) at ambient air. Anaerobic medium was kept in anaerobic jar. The plates were held for 72 hours before declaring them negative. Pathogen identification was done by colony configuration, Gram staining, biochemical reactions i.e., Catalase test, Coagulase, DNAse, Oxidase, Motility, API (Analytical Profile Index) (20E) and API (Coryne) appropriate for gram positive and negative cocci/rods. McFarland 0.5 suspension of all isolated bacterial pathogens was inoculated on Muller Hinton agar plate. The Kirby-Bauer disc diffusion method was employed to administer antimicrobial sensitivity discs tailored to specific isolated pathogens, following the guidelines specified in the 2018 document from the Clinical Laboratory Standard Institute (CLSI). For Polymixin B susceptibility testing broth microdilution was performed on automated system Vitek 2. *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used as control organisms. The analysis of data was conducted utilizing Statistical Package for the Social Sciences (SPSS) version 24.00 and MS Excel 2016 software. For continuous variables, the mean ± standard deviation (SD) was computed, while categorical variables were assessed in terms of frequency and percentage. Chi-square tests and t-tests were employed, with significance set at a p-value ≤ 0.05.

RESULTS

Average age in this research was 31.95 ± 8.95 years. Most 52 (54.74%) of the patient's age were >30 years old. 64 (67.37%) of 95 patients were males and 31 (32.63%) were females, resulting in males to female's ratio of 2.2:1.

Among the *Staphylococcus* spp., 11 isolates were Coagulase Negative *Staphylococci*, 8 isolates were Methicillin Resistant Coagulase Negative *Staphylococci* and 9 isolates were *Staphylococcus aureus* of which 5 were MRSA. To go in details, mixed infections included *Acinetobacter baumanii* and *Pseudomonas aeruginosa*, Coagulase negative *Staphylococci* and *Staphylococcus aureus*, *Morganella morganii* and *Stenotrophomonas maltophila*, *Escherichia coli* and *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Acinetobacter baumanii*, Coagulase negative *Staphylococci* and *Burkholderia cepacia*. Among *Candida* species one of the isolates was identified as *Candida albicans* and the other as *Candida tropicalis*. Among *Pseudomonas* Spp, 7 isolates were *Pseudomonas aeruginosa* and one was *Pseudomonas stutzeri*. All enterococci were identified as *Enterococcus faecalis*. Ventriculoperitoneal shunts and EVD were used in our patient population.

The antimicrobial susceptibility pattern of various Gram positive and Gram-negative pathogens isolated from central nervous system shunt related infections is shown in Table-2 and 3.

Table-1: Frequency of various pathogens isolated from central nervous system shunt related infections.

Bacterial pathogens	No. of Isolates n (%)
Staphylococcus spp.	28 (29.47)
Escherichia coli	16 (16.84)
Acinetobacter baumanii	13 (13.68)
Klebsiella pneumonia	10 (10.53)
Pseudomonas spp.	08 (8.42)
Enterococcus spp.	07 (7.37)
Morganella morganii	02 (2.11)
Enterobacter cloacae	02 (2.11)
Candida spp.	02 (2.11)
Stenotrophomanas maltophila	01 (1.05)

Table-2: Antibiotic susceptibility pattern of Gram-negative bacteria isolated from central nervous system shunt related infections (n= 60).

Antibiotic	Sensitive	Resistant
Ampicillin	21 (35%)	39 (65%)
Cefipime	33 (55%)	27 (45%)
Ceftriaxone	30 (50%)	30 (50%)
Meropenem	56 (93.33%)	04 (6.67%)
Gentamicin	21 (35%)	39 (65%)
Polymixin	57(95%)	3(5%)

Table-3: Antibiotic susceptibility pattern of Gram-positive bacteria isolated from central nervous system shunt related infections (n= 39).

Antibiotic	Sensitive	Resistant
Penicillin	14 (40%)	21 (60%)
Ampicillin	14 (40%)	21 (60%)
Linezolid	35 (100%)	0 (0%)
Cloxacillin	19 (54.28%)	16 (45.71%)
Vancomycin	35 (100%)	0 (0%)
Gentamicin	12 (34.28%)	23 (65.71%)

DISCUSSION

Central nervous system (CNS) shunt surgery is the most common treatment modality in diagnosed cases of hydrocephalus.[9] One of the most dreadful complications associated with shunt placement, is an infected shunt which is responsible for shunt failure and chronic poor-health.[10] Different figures in literature for CNS shunt infection have been reported, and there are considerable variations internationally. Post-operative infection of cerebrospinal fluid (CSF) shunts ranges from 2% to 27%.[11,12] Shunt infection may be defined as detecting pathogens in shunt fluid, the shunt tube, reservoir, and/or blood culture, in conjunction with clinical manifestations indicative of shunt infection, including fever, peritonitis, meningitis, signs of infection of shunt tract, or nonspecific symptoms like headache, vomiting, or altered consciousness.[13]

Despite of recent developments in technology and availability of new antibacterial agents, Infection is still another very common and serious side effects of CSF shunts.[12] Shunt infections develops via colonization of shunt with skin flora and organisms are usually introduced during perioperative period.[10] Coagulase-negative *Staphylococci* (CoNS), most important being *Staphylococcus epidermidis* followed by *Staphylococcus aureus* are taken to be the most common etiological pathogens responsible for shunt infection.[14–17] These studies demonstrate around 50% of all shunt infections are due to Coagulase Negative Staphylococci and 25% are due to *Staphylococcus aureus* with increasing prevalence of Methicillin Resistance *Staphylococci*.[18,19] A retrospective study in Royal hospital for sick children in York hill demonstrated that out of 308 shunt operations 28 episodes of infection were noted making incidence of infection to be 9%. The primary source of infection was Coagulase-negative *Staphylococci*, constituting 44%. Notably, there was a low sensitivity to flucloxacillin and gentamicin among Gram-positive strains, at 22% and 14%, respectively. Resistance to gentamicin was observed in 87% of coagulase-negative *Staphylococci*, while 81% exhibited resistance to flucloxacillin.[17]

A study conducted in China by Xing Wu *et al* showed a trend shift to gram negatives with *Acinetobacter baumanii* as emerging pathogen in neurosurgery units followed by *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Gram-negative rods, repeatedly isolated pathogens responsible for 58% of infective episodes, followed by *S.aureus*, *S. epidermidis* and *Staphylococcus haemolyticus*. Shunt removal and intravenous antibiotics therapy resulted in improved survival of patients to 82%. The large percentage of the isolated bacteria exhibited vancomycin and carbapenem sensitivity. In two other experiments, Gram-negative bacteria caused 7–24% of all ventriculoperitoneal shunt infestations.[22,23] A study in Kenya showed that *Staphylococcus* species were the source of 51% of infections, whereas in 40% of cases, the[20] infection was attributable to gram-negative bacilli. Cefazolin demonstrated susceptibility against each *Staphylococcus aureus* infection and 79% of other *Staphylococcus* infections.[21]

In our study the main etiology of shunt infections are gram-negative rods. This is in contrast to other studies, which reported the most common pathogens to be gram-positive bacteria. [16,17,19] The elevated Gram-negative bacterial infection percentage in this research can be speculated as most device related infections are caused by nosocomial Gram-negative rods and they colonized patient population contributing to CSF shunt infections in Neurosurgery units.[22] Most of Gram-negative bacilli exhibited resistant to three or more categories of antibacterial agents, and were sensitive to Polymixin B and meropenem.[9] Considering the resistance pattern of these isolates in our setup, a combination potent antibiotic such as Vancomycin and meropenem or cefipime is highly recommended, as these antimicrobials will have adequate gram-negative and gram-positive coverage.[20]

Limitations of this study are that prevention of shunt related infections was not addressed. Moreover, risk factors associated with shunt infections were not taken in to consideration.

The eradication of CSF shunt infections has always been a challenge to the treating Neurosurgeon. Outcome can be improved by early recognition of CSF shunt infection along with appropriate use of antimicrobials to achieve CSF sterility. The paradigm shifts in pattern of organisms causing shunt infections is significant and more studies must be taken to achieve better understanding.

CONCLUSION

The study concludes high proportion of Gram-negative infections in our setup which is different from western data. Our study established that the most frequent Gram-negative bacteria isolated from infections related to central nervous system shunts were *Escherichia coli, Acinetobacter baumannii, Klebsiella pneumoniae, and Pseudomonas aeruginosa*, with Meropenem and Vancomycin being appropriate coverage for treatment of Gram-negative and Gram-positive isolates respectively. So, we recommend that proper causative organism should be identified in these particular patients before starting any antimicrobial therapy in an effort to lower death and disability.

AUTHOR CONTRIBUTION:

Rafia Irfan: Conception, research analysis and manuscript drafting.

Gohar Zaman: Data collection, research supervision.

Irfan Ali Mirza: Research analysis and final approval of the draft.

Uzma Qamar: Research analysis and final approval of the version to be published.

Zunera Sajjad: Research supervision and analysis

Azka Zulfiqar: Data interpretation and drafting.

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