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COEXISTING BACTERIAL MENINGITIS WITH URINARY TRACT INFECTION IN CHILDREN LESS THAN 5 YEARS OLD IN CENTRAL CHILD TEACHING HOSPITAL

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ABSTRACT

Objective: To determine age-stratified prevalence of concomitant bacterial meningitis in children <5 years with a urinary tract infection, to determine the prevalence of invasive UTI and risk of meningitis following bacteremia. **Method:** we performed a case series study on patients admitted to our hospital suffering from UTIaged < 5 years old in the central child teaching hospital from April to November 2018. UTI was defined as a urine culture growing ≥10 000 colony-forming units/ml of a single organism from a catheterized specimen or ≥100 000 colony-forming units/ml of a single organism from a bagged urine specimen. Meningitis was defined as cerebrospinal fluid with >35 WBC /mm^3 in infants ≤ one month of age or with >10 WBC /mm^3 in infants >1 month of age. **Results:** Of 100 infants with UTI, a lumbar puncture was performed in 29, and 22 (75%) hadmeningitis. In 11 patients (11%) the meningitis followed UTI while in another 11 patients with meningitis, the UTI was discovered during septic screen.10 patients had bacteremia and 7 of them (70%) developed meningitis. Of 12 patients aged < 1month in the study population (75%) got meningitis together with UTI, the most prevalent isolated pathogen in study population was E. coli in urine (60%) and blood (27%) most of them (54%) were multiple drug resistant infection. 24% of patients with undernutrition developed meningitis. Neutropenia found to be significantly associated with getting gram negative meningitis (p value= 0.001), there was significant association between fever and meningitis (p value= 0.032) but no significant association with gender or anemia (p value = 0.216, 0.791) respectively. **Conclusion:** The clinicians should have a low threshold to perform a lumbar puncture in neonates with UTI, as the risk of getting meningitis is not insignificant in this age group. UTI is a serious infection, and when treated, it should be treated carefully because in most of our cases the isolated pathogen was resistant to the traditional treatment prescribed by physicians, and neutropenia refers indirectly that the patient may develop sever infections.

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INTRODUCTION

Urinary tract infection (UTI) is one of the most common serious bacterial illness in children, especially in infants and young children (Tseng, 2008), the reported incidence of UTI is in girls 7% and 2% in boys in the first six years of life (Craig, 2009). Accurate diagnosis of UTI has important clinical implications; most febrile infants with UTI show evidence of renal parenchymal involvement (pyelonephritis) (Hoberman, 2003). Nevertheless, the presenting signs and symptoms of UTI in childhood are often nonspecific and, among infants, definitive testing for UTI involves bladder catheterization. Accordingly, clinicians caring for young children arefrequently faced with the decision of whether or not to obtain a urine sample for urinalysis and culture (Moro Shaikh, 2008). The studies vary in their definition of UTI, method of urine collection, and eligibility criteria. A number of host factors predispose children to UTI; these include obstructive uropathy, urolithiasis, incomplete emptying of the bladder with residual urine, noncircumcision in boys, female sex after infancy, and constipation (Uwaezuoke, 2003). Previous studies show that bacteremia in association with UTI is not uncommon in infants, occurring in 4% to 10% (Schnadower, 2010). As meningitis is generally the result of dissemination of bacteria via the bloodstream and subsequent penetration of the blood-brain barrier (Kim, 2010), it has been suggested that

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young children with UTI are therefore at higher risk of co-existing meningitis. Accurately determining the rate of co-existing meningitis in children with UTI is clinically highly relevant[8].Identification of co-existing meningitis is critically important, as failure to diagnose central nervous system (CNS) infection may result in partial or incomplete treatment, particularly in view of the fact that several national guidelines suggest that uncomplicated UTI in children can be treated with short courses of oral antibiotics, some of which have poor CNS penetration (Tebruegge, 2011).

Definitions

Urinary tract infection: can be defined as the presence of actively multiplying organisms within the urinary tract (McIntosh, 2008). Urinary tract infection could be referred to as the finding of microorganisms in the urine with or without clinical symptoms and with or without evidence of renal disease. Truly symptom-less bacteriuria may be found on a follow –up culture after infection, or by screening.

Significant bacteriuria: a pure growth of > 10^5 of same organism per ml of clean freshly passed urine. Any growth from urine obtained by correctly performed suprapubic punctures (McIntosh, 2008).

Asymptomatic bacteriuria (covert bacteria): This is the preferred term for children found to have significant bacteriuria in the absence of symptoms related to urinary tract.[11] the majority of children detected during screening program have bacteriuria (Coates, 2015).

Pyuria: Pyuria is defined as the presence of white blood cells (WBCs) in a person's urine (Adegoke, 2012).

Invasive urinary tract infection: it is an infection where bacteremia occurred as a complication of UTI.

Recurrent Urinary Tract Infections: at least two episodes per year and include:

a) Reinfection.
b) Relapse.
c) Persistent infection.

Classification of Urinary Tract Infections: The urinary tract is an anatomical unit, infection of one part readily spreads to involve other part. Although symptoms particularly in childhood, are not liable guide either to the presence of infection or it's localization (Coates, 2016).

A number of clinical syndromes can be delinated as follows:

Urethritis; which is more common in girls.

Cystitis : which could be bacterial or a bacterial.

Acute pyelonephritis; which is an infection involving the renal tissue. There is usually raised ESR, WBC count and C reactive protein, and reduced renal concentrating capacity. In children, pyelonephritis exposes to systemic complications and renal sequel.

Causative organisms of UTI: The usual microbial pathogens isolated from UTI could be as following (Qureshi, 2005):

Escherichia coli	70%
Klebsiellaspp	13%
Proteus spp	11%
Pseudomonas aeruginosa	1%
Enterococci	1-2%
Candida albicans	1-2%

It could be seen from the list, that E. coli constitute the most common pathogen encountered in UTI[10]. Theories have been presented to explain the predominance of E. coli in UTI are[10]. The more predominance of E. coli in the fecal flora which implies that thereis defect in normal host defense mechanism which permit fecal bacteria to ascend through the urinary tract. An important susceptibility factor responsible for the predominance of E. coli is its ability to attach to the urinary tract urothelium[14]. Viral infection of the urinary tract is usually confined to the bladder and haemorrhagic cystitis may occur during an acute viral illness. It may temporarily increase the bladder susceptibility to bacterial infection[10]. Other organisms that gain access to the urinary tract and produce infection are usually associated with instrumentation and invasive procedures.

Pathogenesis of urinary tract infection:-Almost all UTIs are ascending in origin, the bacteria arise from the fecal flora, colonize the perineum, and enter the bladder via the urethra. in uncircumcised males, the bacterial pathogen arise from the prepuce. In some cases the bacteria causing cystitis ascend to the kidney to cause pyelonephritis (Coates, 2016).

Presentation of urinary tract infection:-Clinical signs and symptoms of UTI depend on the age of the child, newborns with UTI may present with jaundice, sepsis, failure to thrive, vomiting or fever. In infants and young children, typical signs and symptoms include fever, foul smelling urine, hematuria, abdominal or flank pain, and new onset urinary incontinence. In school aged children they may have symptoms similar to adults including dysuria, urgency and frequency (White, 2011).

Diagnostic test: Dipstick tests for UTI include leukocyte esterase, nitrite, blood, and protein. Leukocyte esterase is the most sensitive single test in children with a suspected UTI[15].All febrile children between two and 24 months of age with no obvious cause of infection should be evaluated for UTI, with the exception of circumcised boys older than 12 months. Older children should be evaluated if the clinical presentation points toward a urinary source. Urinalysis and urine culture should be obtained from children <3 years of age with a fever (>39.0°C rectal) with no apparent source. For children ≥3 years of age, the presence of urinary symptoms (dysuria, urinary frequency, hematuria, abdominal pain, back pain or new daytime incontinence) can be used as a criterion for requesting a urinalysis and culture (Shaikh, 2007).

Urine collection: A number of methods are available for obtaining satisfactory samples of urine from infants and children, in young children, urine samples collected with a bag are unreliable compared with samples collected with a catheter (Etoubleau, 2009).

Urine examination: Urine analysis must be obtained from the same specimen as that cultured. Pyuria (leukocytes in urine) suggests infection but infection may occur in the absence of pyuria, so this finding is more confirmatory than diagnostic;

conversely, pyuria may be present without urinary infection (Coates, 2016). A concentration more than 10 WBC per cubic milliliter indicates a raised white blood cell excretion rate.

Urine culture: The bacterial count per milliliter is determined; its interpretation depends on the mode of acquisition of the sample. The diagnosis of a urinary tract infection requires the demonstration of at least 10^5 organisms/mL in a bag sample. if culture shows >50000 colonies of single pathogen or if there are 10000 colonies and the child is symptomatic, the child is considered to have a UTI (Coates, 2016).

Culture revealing multiple species: usually represent results from contaminated urine sample, therefore, the culture must be repeated with more care in collection of specimens.

Complications of UTI

Bacteremia and UTI: Several studies have demonstrated that bacteremia occurs infrequently in children with UTIs (Schnadower, 2010) and that children with bacteremia are difficult to distinguish clinically from children with nonbacteremic UTIs. The prevalence of bacteremia in infants with UTI decreases with age and is low after 6 months of age (Roman, 2015). Clinical practice guidelines exist for the diagnosis and management of UTIs in young children[19] but do not include recommendations regarding when to obtain blood cultures in children with suspected UTI or appropriate treatment regimens for infants with UTI and bacteremia, which generates considerable uncertainty over how to manage these infants (Roman, 2015). In neonates, neonatal septicemia or meningitis caused by Escherichia coli and other gram negative bacilli cannot be differentiated clinically from septicemia or meningitis caused by other organisms. The early signs of sepsis can be subtle and similar to signs observed in noninfectious processes (Kimberlin, 2018).

Antimicrobial treatment

Treatment of acute infection: Once the diagnosis of UTI has been confirmed prompt treatment should be initiated, if the child is febrile and deemed appropriate to receive empiric treatment prior to urine culture results, antibiotic treatment should be implemented. Treatment should include 7–14 days of antimicrobials according to local sensitivity patterns. In regards to treatment duration, NICE guidelines recommend antibiotic therapy for 7–10 days[21].In both the AAP and NICE guidelines, oral or parenteral antibiotics were found to be equally effective. If a child is ill and unable to tolerate oral antibiotics, a course of parenteral antibiotics for 2–4 days followed by oral antibiotics is sufficient (Roberts, 2011). Antibiotics used for treatment of UTI are listed in Table (1). The initial choice of antibiotic should be guided by knowledge of local resistance patterns. Cefixime is a common choice for a first febrile UTI, pending susceptibilities.

Bacterial meningitis: Bacterial meningitis is associated with high mortality and morbidity, reaching 15% and 50%, respectively, especially during the neonatal period (Gaschignard, 2011; Houdouin; 2008 and Okike, 2014). Escherichia coli is the first cause of bacterial meningitis in preterm infants and the second cause after group B streptococci in term infants (Gaschignard, 2011 and Okike *et al*., 2014).

Table 1. Antibiotics commonly used to treat urinary tract infections (UTIs) if the isolate is susceptible (Robinson, 2014)

Parenteral antibiotics	
Drug	Dosage per day
Ampicillin	200 mg/kg IV/day (divided every 6 h)
Ceftriaxone	50–75 mg/kg IV/IM every 24 h
Cefotaxime	150 mg/kg/day IV (divided every 6 h or 8 h)
Gentamicin	5–7.5 mg/kg IV/IM once per day
Tobramycin	5–7.5 mg/kg once per day
Oral antibiotics	
Amoxicillin	50 mg/kg/day (divided in three doses)
Amoxicillin/clavulanate	(7:1 formulation) 40 mg/kg/day (divided in three doses)
Co-trimoxazole	8 mg/kg/day of the trimethoprim component, divided in two doses (0.5 mL/kg/dose)
Cefixime	8 mg/kg/day (given as a single dose)
Cefprozil	30 mg/kg/day (divided in two doses)
Cephalexin	50 mg/kg/day (divided in four doses)
Ciprofloxacin	30 mg/g/day (divided in two doses)

Definition of bacterial meningitis: Meningitis is the acute inflammation of the meninges, subarachnoid space, and brain vasculature resulting from infection (Barichello, 2013), whileneonatal meningitis is categorized as early and late onset, which is defined by the presence of signs of infection and organism isolation from cerebrospinal fluid (CSF) cultures at ≤72 hours and >72 hours of life, respectively (Shane, 2013). The clinical symptoms and signs of bacterial meningitis in children vary depending on the age of the child and duration of disease. Classical signs and symptoms of bacterial meningitis consisting of fever, altered mental status and neck stiffness are less frequently present in younger infants compared to older children and adults. Typically, childhood bacterial meningitis begins with fever, chills, vomiting, photophobia and severe headache (Snaebjarnardóttir, 2013).

Causative organisms: Common pathogens of meningitis in neonates mainly are (Miall, 2015):

Early onset meningitis: including

- Group B Streptococcus: responsible for >40% of all early-onset infections (Heath, 2012)
- E. coli : is the second most common pathogen and is isolated in 30% of all early-onset infections (Stoll, 2011), Since the 1990s, E. coli has emerged as the most common cause of early-onset sepsis and meningitis among VLBW infants (VLBW, <1500 g birth weight) infants (Camacho-Gonzalez, 2013 and Bizzarro, 2008)
- S. pneumonia.

Klebsiella sp., Enterococcus sp., E. coli, Enterobacter sp., and Pseudomonas sp. In late onset meningitis. Staphylococcus epidermidis and other coagulase-negative staphylococci frequently cause meningitis and CSF shunt infection in patients with hydrocephalus or those who have undergone neurosurgical procedures. Immunocompromised children can develop meningitis caused by Serratia, Proteus, and diphtheroids.

Risk factors for bacterial meningitis

1. Risk factors for the development of neonatal meningitis are similar to neonatal sepsis which include:
   - Prematurity
   - VLBW (<1500 g)

- Prolonged hospitalization
- Presence of external devices (e.g., reservoirs, shunts, catheters) and maternal related factors like (chorioamnionitis, premature and prolonged rupture of membranes, rectovaginal colonization of GBS) (Mukhopadhyay, 2012; Cohen-Wolkowiez, 2009 and Heath, 2010).

Risk factors beyond the neonatal period (Coates, 2016):

- A major risk factor is the lack of immunity to specific pathogens associated with age.
- Recent colonization with pathogenic bacteria
- Close contact with individuals having invasive disease
- Crowding, poverty
- Male gender

Pathogenesis of bacterial meningitis: Pathogens enter the central nervous compartmentseither through the blood–brain barrieror blood–cerebrospinal fluid (CSF) barrier (Schwerk, 2010). The blood–brain barrier is a structural and functional barrier that is formed by brain microvascular endothelial cells which protects the brain from any microbes and toxins circulating in the blood. However, meningitis-causing pathogens, including E coli, group B streptococcus, S, pneumonia, and N. meningitides, have been shown to cross the blood–brain barrier as live bacteria (Kim, 2010). Bacterial meningitis proceeds through distinct phases: a) colonization or mucosal invasion, b) intravascular survival and multiplication, c) crossing of the blood brain barrier, d) invasion of the meninges and the CNS, e) release of pro-inflammatory cytokines, f) neuronal injury. The absence of opsonic or bactericidal antibodies is an important risk factor in most cases of meningitis caused by GBS, E. Coli, LM, Hib, S. pneumonia and N. meningitides (Berardi, 2010).Studies in humans and in experimental animals have showed that there is a relationship between the magnitude of bacteremia and the development of meningitis (Kim, 2010 and Kim, 2003).

Clinical presentation: The younger the child, the less likely he or she is to exhibit the classic symptoms of fever, headache, and meningeal signs.

Neonates: Neonates with bacterial meningitis often present with non-specific signs and symptoms (Galiza, 2009) CSF examination can-not rule out the possibility of meningitis in these patients, soempirical antimicrobial therapy should be initiated based onlow clinical suspicion and should be continued until CSFculture results are negative (Malbon, 2006). Neonateswith bacterial meningitis often present with nonspecific symptoms such as irritability, poor feeding, respiratory distress, paleor marble skin and hyper- or hypotonia (Okike, 2014 and Kavuncuoğlu, 2013) Fever ispresent in a minority (6–39%) of cases. Seizures are reported in 9–34% of cases and are more commonly reported among thosewith group B streptococcal (GBS) compared toE. colimeningitis. Respiratory distress or failure is frequently reported asone of the initial symptoms of neonatal meningitis (Okike, 2014 and Kavuncuoğlu, 2013).

Infants: Clinical characteristics of bacterial meningitis in children beyond neonatal age, classical signs and symptoms of bacterial meningitis consisting of fever, altered mental status and neckstiffness areless frequently present in younger infants compared to older children. Typically, childhood bacterial meningitis begins with fever, chills, vomiting, photo-phobia and severe headache (Snaebjarnardóttir, 2013 and Franco-Paredes, 2008). Feveris the most commonly reported symptom in childhood bacterial meningitis, with an occurrence rate of 92–93%. Vomiting is reported in 55–67% of children with bacterial meningitis (Snaebjarnardóttir, 2013 and Franco-Paredes, 2008).

Work up: In developing countries, the most commonly used approaches for detection and characterization of bacterial meningitis pathogens include culture, Gram stain, and latex agglutination. Although culture is considered the gold standard for case confirmation in clinics, the positive rate is relatively low due to suboptimal storage and transportation conditions, culture practice, and/or antibiotic treatment administered before the specimen is collected (Prevention, 2014). A firm diagnosis is usually made when bacteria are isolated from the cerebrospinal fluid (CSF) and evidence of meningeal inflammation is demonstrated by increased pleocytosis, elevated protein level, and low glucose level in the CSF.

Timely collection and processing of CSF and isolation of an organism allows optimization of choice of antimicrobial agent and duration of therapy. CSF chemistries and cytology vary, depending on the maturity and age of the newborn (Ku, 2015). A lumbar puncture (LP) may be contraindicated in some of the following conditions: unstable patients with hypotension or respiratory distress who may not be able to tolerate the procedure, brain abscess, brain tumors or other cause of raised intracranial pressure, and occasionally infection at the lumbar puncture site. Blood studies that may be indicated include the following: CBC with differential, Blood cultures, coagulation studies, serum glucose and electrolytes. Measurement of the serum glucose level close to the time of CSF collection is helpful for interpreting CSF glucose levels and assessing the likelihood of meningitis.

PCR: PCR may also be used to detect microbial DNA in CSF. It also has the advantage of being relatively rapid and is able to detect low amounts of bacteria in the CSF (Welinder-Olsson, 2007) and although not 100% specific, some studies have found PCR to have 100% sensitivity, allowing antibiotics to be ceased if PCR is negative. And it is more sensitive than CSF culture, particularly in patients who received previous antimicrobials (Bøving, 2009). Traditional real-time PCR (rt-PCR) tests with high sensitivity and specificity have been implemented in many public health laboratories for the detection of pathogens (Wang, 2011 and Wang, 2011), The implementation of PCR assays for diagnostic purposes became absolutely essential due to a change in clinical management over the last decade. It is important to point out that fewer lumbar punctures are performed at presentation and prompt antibiotic therapy is advisable in pyrexial patients with a suggestive rash; this has contributed to a significant fall in the number of culture confirmed cases (Tuyama, 2008).

Lumbar Puncture and CSF Analysis: - Definitive diagnosis is based on examination of CSF obtained via lumbar puncture. Opening and closing pressures should be measured in the cooperative patient. Similarly, the color of the CSF (eg, turbid, clear, or bloody) should be recorded. If the CSF is not crystal clear, administer treatment immediately without waiting for the results of CSF tests.

Table 2. Antibiotics used for treatment of meningitis

Antibiotic	Susceptible Bacteria	Notes
Penicillin G[20]	GBS	Monotherapy acceptable if GBS confirmed by culture and clinical improvement is observed
Ampicillin[57,58]	GBS L. Monocytogenes Enterococcus spp.	17–78% of E. coli isolates resistant Poor CNS penetration Requires higher doses for meningitis
Gentamicin[58,59]	E. coli Klebsiella sp. Enterobacter sp. Pseudomonas sp. Citrobacter sp. Serratia sp.	Poor CNS penetration Synergistic effect with ampicillin in treatment of L. monocytogenes Pseudomonas sp. may require combination therapy with a second agent Requires therapeutic drug monitoring
Cefotaxime[32,58]	E. coli Klebsiella sp. Enterobacter sp. Citrobacter sp. Serratia sp.	Good CNS penetration Used instead of gentamicin in cases of suspected or confirmed meningitis Not active against L. monocytogenes or Enterococcus sp.
Meropenem[20,60]	E. coli Klebsiella sp. Enterobacter sp. Citrobacter sp. Serratia sp. Pseudomonas sp.	Good CNS penetration Limit use to multidrug resistant organisms (e.g., extended-spectrum beta-lactamase-producing organisms)

Characteristic CSF findings for bacterialmeningitis consist of polymorphonuclearpleocytosis, low sugar level, and raised CSF protein levels (Van de Beek, 2006).

CSF studies: lumbar puncture (LP) is necessary for the definitive diagnosis of bacterial meningitis and should be performed where a clinical suspicion for meningitis exists, Initial analysis of the CSF should include microscopy with gram stain, culture and measurement of protein, and glucose levels. Contraindication for lumbar puncture include signs of raised intracranial pressure, such as an alteration in level of consciousness, papilloedema, prolonged seizures, or focal neurological signs, as well as coagulation disorders, cardiorespiratory instability, a history of immunosuppression, certain central nervous syndrome (CNS) conditions, or localised infection at the site of insertion of the lumbar puncture needle (Tacon, 2012). The CSF leukocyte count in bacterial meningitis usually is elevated to >1000 per cubic millimeter and,typically, there is a neutrophilic predominance (75-95%). turbid CSF is present when the CSF leukocyte count exceeds 200-400/mm^3, normal healthy neonates may have as many as 30 leukocytes/mm^3(usually <10) (Coates, 2016). CSF protein is typically elevated (100–200 mg/dL) and glucose low (CSF to serum ratio <0.4). While the presence of an organism on gram stain, or culture of bacteria from the CSF, is diagnostic of bacterial meningitis, a number of other investigations may also be performed on CSF to aid diagnosis. Latex agglutination may be performed to detect the presence of bacterial antigens in the CSF. It has the advantage of being able to be rapidly performed, with a result available in less than 15 minutes, well before culture results are available (Tacon, 2012).

Other Laboratory Investigations-Blood cultures should be performed in all patients with suspected bacterial meningitis. They may be of particular value if a lumbar puncture is contraindicated. The likelihood of a positive blood culture result varies with the infecting organism (Brouwer, 2010).

Treatment

Supportive treatment: Any child with a diagnosis of bacterial meningitis will need supportive therapy, which may include cardiorespiratory support in a pediatric intensive care unit and directed management of complications, such as seizures, cerebral edema, SIADH, DIC, or shock. Early, protocolized, aggressive care by a consultant supervised paediatric team improves survival and outcomes (Tacon, 2012). A recent Cochrane meta-analysis found some evidence to support the use of maintenance, rather than restrictive fluids in the first 48 hours (Maconochie, 2008).

Antibiotic treatment: As soon as bacterial meningitis is diagnosed (actually or presumptively), IV access should be secured and appropriate antimicrobial drugs (and possibly corticosteroids) should be given. The choice of antibiotic depends on the organism isolated. In most cases the initial treatment has to be empirical, but nonetheless based on epidemiological knowledge of the commonest organisms for each age group and local antibiotic resistance patterns. The chosen antibiotic should have bactericidal activity in the CSF. Patients with pneumococcal or Gram negative bacillary meningitis who are treated with bacteriostatic antibiotics may have a poor clinical outcome (El Bashir, 2003).

Empiric antibiotic treatment: The choice of empiric antibiotic treatment is conditional on the age of the patient and the regionalrate of decreased susceptibility to penicillin and third-generationcephalosporins of S. Pneumonia. When there is arisk of decreased susceptibility of S. pneumonia, empiric treatment should include vancomycin or rifampicin. However, someexperts advise the use of ceftriaxone or cefotaxime as empiric treatment instead of vancomycin or rifampicin when true resis-tance to third-generation cephalosporin.

Specific antibiotic treatment after identification of causative micro-organism: After identification of the pathogen through cultureand antibiotic susceptibility testing, the antibiotic treatment canbe optimized. Prompt initiation of antibiotics is critical. Delays in treatment are associated with increased mortality and morbidity (Weisfelt, 2007). Upon identification of the pathogen and its susceptibilities, antimicrobial coverage should be adjusted accordingly. Table (2) shows the antibiotics used to treat meningitis according to pathogen.

Duration of antimicrobial therapy: The optimal duration of antibiotictreatment for bacterial meningitis has been studied in sixrandomized clinical trials in children.

A meta-analysis of these trials concluded that there was insufficient evidence to advisea short course of antibiotics (A Karageorgopoulos, 2009). AlargeRCTshoweda5-dayregimen was as effective as 10 days of antibiotics in children with bacterial meningitis who were in a stable condition after3 days of treatment (Van de Beek, 2016).

- N meningitidis - 7 days
- H influenzae– 7-10 days
- S pneumoniae - 10-14 days
- Aerobic gram-negative bacilli - 21 days or 2 weeks beyond the first sterile culture (whichever is longer)
- |L monocytogenes - 21 days or longer.

It has been found that there were no differences between short-course (4-7 days) and long-course (7-14 days) treatment with IV ceftriaxone were demonstrated with respect to end-of-therapy clinical success, long-term neurologic complications, long-term hearing impairment, total adverse events, and secondary nosocomial infections (AKarageorgopoulos, 2009). However, the AAP does not endorse courses of therapy shorter than 5-7 days for meningococcus, 10 days for H influenza, and 14 days for S. pneumonia. Although the available evidence is limited, some studies show no difference between short-course and long-course antibiotic regimens for treatment of bacterial meningitis in children (van de Beek, 2010).

Etiology of bacteremia in infants: It is estimated that 2% of infants presenting with fever without a source will have bacteremia, but it is often difficult to clinically predict which infants have bacteremia before obtaining blood culture results (Greenhow, 2012 and Watt, 2010), Recent data suggest that the epidemiology of bacteremia in term infants is shifting, and that Escherichia coli is now the most common cause of bacteremia in febrile infants ≤90 days old (Greenhow, 2012). Severe infections, specifically pneumonia, meningitis and sepsis, have been estimated to be responsible for 23% of the approximately 3 million global neonatal deaths that occur annually; an even larger proportion of neonatal and young infant fatalities due to serious bacterial infections may occur in high-burden community settings (Liu, 2012). Acute infections are a common reason for presentation to the children's emergency department (ED) (Sands, 2012). In young children presenting with an acute febrile illness, serious bacterial infection occurs in 7%. Bacteremia occurs in 1 in 250 febrile children aged <5 years and may be difficult to recognize (Craig, 2010). Determining the primary source of infection is critical in the management of a patient with bacteremia, as well as in the identification of the affected patient population. Untreated urinary tract infections most commonly cause community-acquired bacteremia. Soft tissue and intra-abdominal infections are not as common and are more prevalent in the post-operative surgical setting. Escherichia coli is the most common cause of gram-negative associated bacteremia, while Staphylococcus aureus is the most common gram-positive organism (Munro, 2018 and Woll, 2018).GBS bacteremia is no longer the leading cause of bacteremia but occurs most frequently in the first month of life, and 29% had concomitant meningitis. E coli is now the leading cause of bacteremia, and S aureus follows GBS[64].Most cases of bacteremia (76%) occurred with a source, most frequently from urinary tract infections (34%), gastroenteritis (17%), pneumonias (8%), osteomyelitis (8%), and skin and soft tissue infections (6%) (Greenhow, 2017).

PATIENTS AND METHODS

Study Design: This case series study was conducted in Central Child teaching hospital during the period extended for 7 months from 1st April to 1st November 2018, where children suffering from UTI and/or meningitis were admitted to the ward, a pretested check list was filled through direct interview with the companion of the child. The check list included age, gender, A full history and clinical examination was done, necessary laboratory investigations including CBC, urine culture and sensitivity, blood culture and sensitivity and CSF analysis were done according to the idea of authorized pediatrician. The diagnosis of UTI was made depending on urine culture results only. Association between anemia and getting meningitis was measured, child was considered anemic if Hb level was below the normal value each according to age (Coates, 2016). Association between WBC count and getting meningitis was also measured, patient considered to have leukocytosis if total WBC was more than11,000 per mm^3 Association between neutrophil count and getting meningitis was measured, neutrophilia, normal or neutropenia were considered if absolute neutrophil count was above, equal to or below the normal values respectively, each according to age. Patient was considered to have multiple drug resistant infection if the culture and sensitivity of urine revealed resistance for three or more antibiotics (Magiorakos, 2012). Patient was considered to be febrile if oral or corrected anal or axillary temperature was more than 37.5° C.

Ethical consideration: The proposal of this study was studied and discussed by the scientific and ethical comitee at Arabic board of pediatrics. The agreement of health authority in central child teaching hospital was approved before starting of the study, verbal consent of the person that accompanied the patient was approved before taking information after full explanation of the aim of the study and insuring confidentiality of the collected data which will be anonymous and will not be used but for research purposes.

Statistical analysis: The collected data were introduced into Microsoft excel sheet and loaded into SPSS V24. The descriptive statistics were presented through frequency distribution tables, means and standard deviations and suitable graphs were used accordingly inferential statistics were presented using chi square, fissure exact test and t test to find out significance of associations between related categorical variables and differences between related continuous variable means. P value less than 0.05 was considered as discrimination points of significance.

RESULTS

The results of this case series study showed that 100 patients suffered from UTI were studied, 12% of them were under one month of age, 41% and 47% were aged 1-12 months and 1-5 years respectively. 48% of patients were males, 25% suffered from underweight (Figure 1). Twenty-two percent of studied patient suffered from meningitis. UTI was discovered in 89% of studied patients during septic screen, while 11% got UTI followed by meningitis. fever was found among 58% of cases while hypothermia was found among 5%. anemia was found in 34% of cases (Table 3).

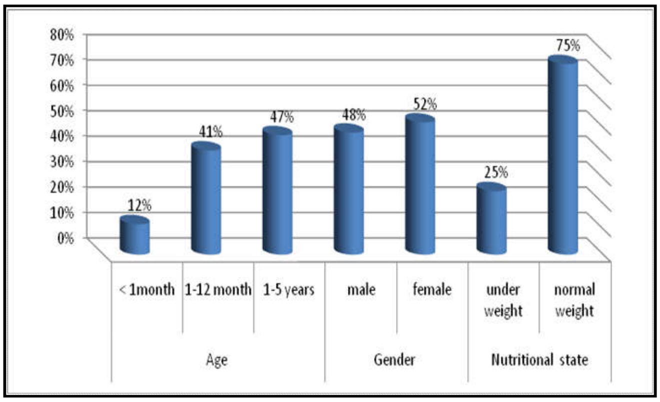

Figure 1. Distribution of studied children according to demographic variables

Table 3. Distribution of studied cases according to diseases

		N	%
Meningitis	No meningitis	78	78%
	Meningitis	22	22%
Disease occurred first	UTI discovered during septic screen	89	89%
	UTI followed by meningitis	11	11%
Fever	Hypothermia	5	5%
	Normal temp	37	37%
	Fever	58	58%
Anemia	Anemia	34	34%
	No anemia	66	66%

As shown in table (4) significant association was noticed between age group and getting meningitis in children suffered from UTI, where 75% of UTI patients aged below one month got meningitis while 10.6% of 1-5 years old UTI patients got meningitis (p-value 0.001

Table 4. Association between age group and meningitis according to Chi square test

		Meningitis		No meningitis		P value
		N	%	N	%	
Age group	< 1month	9	75%	3	25%	0.001
	1-12 month	8	19.5%	33	80.5%	
	>1-5 years	5	10.6%	42	89.4%	

As shown in table (5) no significant association was noticed between gender and getting meningitis (p value= 0.216).

Table 5. Association between gender and meningitis according to Chi square test

Gender	Meningitis		No meningitis		P value
	N	%	N	%	
Male	8	16.7%	40	83.3%	0.216
Female	14	26.9%	38	73.1%	

As shown in table (5) no significant association was noticed between nutritional status and getting meningitis (p value= 0.780).

Table 6. Association between nutritional status and meningitis according to Chi square test

		Meningitis		No meningitis		P value
		N	%	N	%	
nutritional state	Under weight	6	24.0%	19	76.0%	0.780
	normal weight	16	21.3%	59	78.7%	

As shown in Table (6) fever in UTI patients was found to be significantly associated with getting meningitis (p value = 0.032

Table 7. Association between fever and meningitis according to Chi square test

		Meningitis		No meningitis		P value
		N	%	N	%	
Fever	Hypothermia	0	0.0%	5	100.0%	0.032
	Normal temp	4	10.8%	33	89.2%	
	Fever	18	31.0%	40	69.0%	

As shown in table (8) triple antibiotics were prescribed to all patients with meningitis in this study in comparison with only 3.8% of patients received single antibiotics (p value = 0.001).

Table 8. Association between treatment and meningitis according to Chi square test

		Meningitis		No meningitis		P value
Treatment	single AB	2	3.8%	51	96.2%	0.001
	double AB	13	32.5%	27	67.5%	
	triple AB	7	100.0%	0	0.0%	

There was no significant difference between duration of disease in meningitis and no meningitis group (p value 0.512) table (9)

Table 9. Differences between duration of disease and occurrence of meningitis according to independent two sample t test

		N	Mean	Std. Deviation	P value
Duration of disease	Meningitis	22	3.64	1.093	0.512
	No meningitis	78	3.46	1.101	

Table (10) showed that significant association was noticed between neutropenia and getting meningitis while no meningitis cases was associated with either normal neutrophil counts (93.5%) or neutrophilia (61%) in comparison with meningitis group (6.5% and 39%) respectively.

Table 10. Association between blood picture analysis and meningitis according to Chi square test

		Meningitis		No meningitis		
		N	%	N	%	
WBC	Leukocytosis	22	44.9%	27	55.1%	0.001
	Normal	0	0.0%	51	100.0%	
Neutrophil	Neutrophilia	7	39%	11	61%	0.001
	Normal	4	6.50%	58	93.50%	
	neutropenia	11	55.00%	9	45%	
Anemia	Anemia	8	23.5%	26	76.5%	0.791
	Normal	14	21.2%	52	78.8%	

Urine culture showed that 60% of all studied patients got E. Coli infection, 13% pseudomonas, and 10% got Klebsiella infection. While 12.7% of blood cultures showed E. Coli infection. The results of blood and urine cultures of studied patients is shown in Table (11).

Table 11. Distribution of studied patients according to results of urine and blood culture

Urine culture	E.coli	60	60%
	Klebsiella	10	10%
	Pseudomonas	13	13%
	Proteus	6	6%
	Enterobacter	8	8%
	Enterococcus fecalis	3	3%
Blood culture	Negative	53	84%
	E. Coli	8	12.7%
	Pseudomonas	2	3.2

No significant association was noticed between type of UTI and getting meningitis (p value = 0.347) while E. Coli bacteremia was found to be significantly associated with getting meningitis in comparison with pseudomonas bacteria or negative bloodculture (p value 0.032) Table (12). Table (13) showed that among meningitis patients the most common bacteria isolated from urine culture and blood culture was E. coli, 77.3% and 27.3% respectively.

Table (14) shows significant association between multiple drug resistant pathogen isolated in urine culture and getting meningitis as compared to not drug resistant pathogen (p value = 0.001). The total number of meningitis cases admitted to our hospital during the study period was 273 patients, figure (4) shows the rate of associated infection that occurred together with meningitis, it shows that 10% had UTI while 11% had lower respiratory tract infection in form of pneumonia, bronchiolitis or bronchitis.

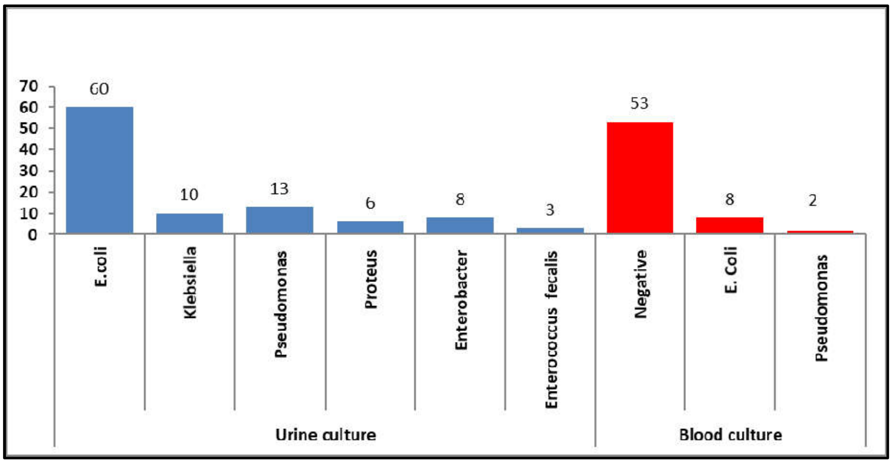

Figure 2. Results of urine and blood cultures done to studied sample

Table 12. Association between results of urine culture or blood culture with meningitis according to Chi square test

		meningitis		no meningitis		
		Count	Row N %	Count	Row N %	
Urine culture	E. Coli	17	28.3%	43	71.7%	0.347
	Klebsiella	0	0.0%	10	100.0%	
	pseudomonas	3	23.1%	10	76.9%	
	Proteus	1	16.7%	5	83.3%	
	Enterobacter	1	12.5%	7	87.5%	
	enterococcus Fecalis	0	0.0%	3	100.0%	
Blood culture	Negative	15	28.3%	38	71.7%	0.032
	E Coli	6	75.0%	2	25.0%	
	Pseudomonas	1	50.0%	1	50.0%	

Table 13. Distribution of meningitis cases according to type of bacteria isolated from urine or blood

Urine culture	E. Coli	17	77.30%
	pseudomonas	3	13.60%
	proteus	1	4.50%
	enterobacter	1	4.50%
Blood culture	negative	15	68.20%
	e.coli	6	27.30%
	pseudomonas	1	4.50%

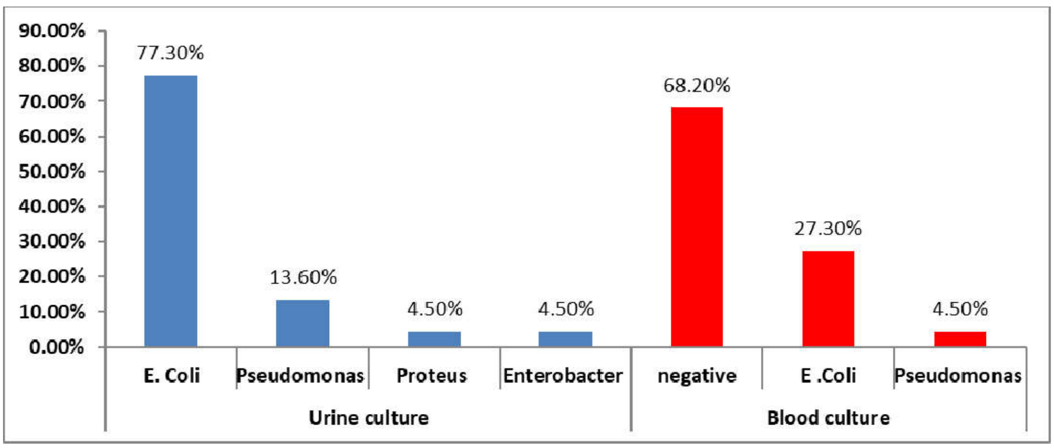

Figure 3. Distribution cases of meningitis cases according to type of bacteria isolated from urine or blood culture

DISCUSSION

Clinicians often grapple with the necessity of performing a lumbar puncture in infants with UTI, weighing the potential harms of an invasive procedure against the risk of missing a case of bacterial meningitis. Prior studies, have reported low rates of concomitant meningitis in infants with UTI, but these studies have been limited by small sample sizes[9]or have excluded the youngest infants. In the absence of reliable data, it remains uncertain whether young children with UTI should always have a lumbar puncture to rule out co-existing meningitis. In this case series study of 100 infants aged ≤ 5 years old with UTI, 22 patients had meningitis and only 7 of them had bacteremia, the prevalence of coexisting meningitis was higher in < 1-month old age group than other age groups. Suggesting that risk of concomitant meningitis for infants with UTI is greatest in the first month of life. Our results are similar to previous studies. In a retrospective, single-center cohort study that included 467 Australian infants 0–2 months of age with culture-confirmed UTI and a paired CSF sample, 2 infants had concomitant bacterial meningitis[8]. Both of these cases occurred in infants <1 month of age; thus, the prevalence of concomitant meningitis for infants <1 month of age was 1.2% (95% CI: 0.15%–4.36%), and for the 1–2 months of age group, it was 0% (95% CI: 0%–1.25%). Similarly, in a multicenter study of 1895 infants 29–60 days of age with UTI, only 2 (0.1%) had concomitant bacterial meningitis[6]. The difference in percentage is due to variation in sample size and age of the study population. In our study, of 100 patients 10 had bacteremia (10%) and this result is similar to previous study done by Newman *et al*, where 3066 infants with fever included in the study, 54% of them had UTI and 10% of those who had UTI developed bacteremia[73]. It is also found that 11 patients were admitted to the hospital as UTI and then developed meningitis all of them were below 2 months old and 5 patients had bacteremia which highly suggest that they developed meningitis following bacteremia. In this study population, twenty patients had low neutrophil count, of them, eleven (55%) developed meningitis, this correlates with the fact that most neutropenic patients develop gram negative infections such as sepsis.

In our study E. coli is the most common isolated pathogen in urine culture and this result is similar to previous study conducted in 23 center retrospective cross sectional study were 23,882 American infants included in the study, and 1737 infants had UTI diagnosed by urine culture and the most common pathogen was E. coli [74].The predominance of E. coli is likely attributed to the more predominance of E. coli in the fecal flora which implies that there is defect in normal host defense mechanism which permit fecal bacteria to ascend through the urinary tract. And an important susceptibility factor responsible for the predominance of E. coli is its ability to attach to the urinary tract urothelium. In our study there were 6 patients (24%) out of 22 with meningitis are underweight this means there is increased risk for getting meningitis in malnourished infants. A study that was conducted in Palestine by A.Al Jarousha *et al* showed significant association between malnutrition and meningitis were 1853 patients with suspected bacterial meningitis were included in the study, 50 patients of them (6%) were underweight[75]. In this study, we found that fifty-four patients (54%) had multiple drug resistant urinary tract infection and most of them had E. coli isolated in urine culture and nineteen patients (86.4%) of them got meningitis. The incidence of antimicrobial-resistant E. coli infections is increasing globally[76], and the emergence of antimicrobial resistance in E. coli has increased faster than the development of new antibiotics, leading to a paucity of therapeutic agents for highly antimicrobial-resistant strains. Our results are close to a study done in Mexico on 110 patients with UTI where the incidence of MDR was 63% [77], the difference in percentage is due to variation in sample size. The percentage of UTI patients among meningitis cases regardless the age that was admitted to our hospital during the study period was 10% which is considered high as compared with other associated infections. Our study has several limitations. First, we don't have data on antibiotic administration before performance of the diagnostic lumbar puncture. Pretreatment with antibiotics may have led to our underestimating the true prevalence of meningitis. Second, blood culture was done in only 63 patients with UTI so we may have underestimated the incidence of bacteremia because in 47 patients, blood culture was not done. Third, by depending on physician documentation to assess clinical appearance and severity of illness, we may have missed some more subtle differences in clinical presentation.

Conclusion

- Urinary tract infection proved by urine culture and complicated by meningitis is more prevalent in less than one-month age group.
- When there is urinary tract infection proved by culture, it should be fully investigated to exclude the bacteremic phase.
- When patient with UTI develop bacteremia, the infection should be dealt with seriously to exclude more serious infections like meningitis.
- Neutropenia refers indirectly that the patient may develop sever infection, for that, they should be fully investigated.
- In UTI caused by E. coli, meningitis and other serious infections should be considered when the patient received the course of infection.
- UTI is a serious infection, and when treated, it should be treated carefuly because in most of our cases the isolated pathogen was resistant to the usual treatment prescribed by physicians like (augmentin, septrin, claforan and ceftriaxone), so, we should treat according to the results of culture and sensitivity.

Recommendation

- Any neonate diagnosed as UTI by culture or depending on signs and symptoms, should be fully investigated to exclude complications
- In case of UTI with bacteremia, LP is considered very important to confirm development of meningitis.
- Neutropenic patients should be dealt with seriously because it indirectly refers to more hidden and dangerous complications such as meningitis.
- Gram negative bacteria, specially E. coli, is the most common cause behind complications.
- Treatment of UTI using traditional antibiotics that are usually prescribed was not scientific without dealing with treatment according to culture and sensitivity test.

- Drawing blood culture to patients with UTI proved by culture, in order not to underestimate more serious complications like meningitis.

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