Common Pathogens Associated with Neonatal Sepsis and Their Antibiotic Resistance Pattern in Sohag University Hospital

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Abstract

Introduction: Neonatal sepsis is defined as a clinical syndrome in an infant 28 days of life or younger, manifested by systemic signs of infection and isolation of a bacterial pathogen from the bloodstream**[EmanShehab El-Din et al, 2015].** Positive blood culture and sensitivity of the isolate is the best guide to antimicrobial therapy and once started should be modified according to the culture sensitivity reports**[Aggarwalet al, 2001]**.

Aim of the work: To determine clinical and microbiological pattern of neonatal sepsis in Sohag university hospital with special focus on causative pathogens and their response to used antimicrobials.

Patient and methods: Our study conducted over a period of 18 months between October 2015 and April 2017 at Sohag university hospital and included 75 neonates with suspected sepsis and positive blood culture using Egyptian neonatal network (EGNN) guidelines, subjected to full clinical examination, septic screen(CBC, ESR and CRP) and blood culture and sensitivity tests.

Results: All studied neonates presented with late onset sepsis with higher incidence in infants born via CS especially with low and very low birth weight**.**The incidence of neonatal sepsis was predominantly due gram negative bacteria mainly Klepseillapneumonae followed by staphylococcus haemolyticusandstaphylococcus epidermidis. Klebseilla isolates showed high sensitivity for aminoglycosides and quinolones antibiotics with resistance to penicillin's group, Staphylococcus isolates showed resistance to penicillin's and aminoglycosides while sensitive to quinolones and nitrofurantions. E.coli and Pseudomonas species showed moderate sensitivity to 3rd generation cephalosporins, aminoglycosides, quinolones and nitrofurantoins with resistance to classic penicillin's.

Conclusion: In our study gram negative bacteria mainly Klepseillapneumonae was the most causative agent of neonatal sepsis. Most isolated organisms showed resistance to classic penicillins.Klepseillapneumonaeshowed high sensitivity for aminoglycosides and quinolones, Staphylococcus isolates showed high sensitivity to quinolones and nitrofurantions while E.coli and Pseudomonas species showed moderate sensitivity to 3rd generation cephalosporins, aminoglycosides, quinolones and nitrofurantoins.

Keywords: Neonatal sepsis, blood culture and sensitivity in neonates, Klebsiella neonatal sepsis, multidrug resistance

Manuscript

Introduction:

Globally, sepsis still one of the major causes of morbidity and mortality in neonates, in spite of recent advances in health care units **[J. H.Wu et al, 2009].** More than 40% of under-five deaths globally occur in the neonatal period, resulting in 3.1 million newborn deaths each year **[UNICEF et al, 2011].**The majority of these deaths usually occur in low-income countries and almost 1 million of these deaths are attributed to infectious causes including neonatal sepsis, meningitis, and pneumonia **[R. E. Black et al, 2010].** On the other hand, the survivors of neonatal sepsis are vulnerable to short and long-term

neurodevelopmental morbidity **[B. J. Stoll et al, 2002 – O. Dammann et al, 2002]**.Sepsis related mortality is largely preventable with rational antimicrobial therapy with aggressive supportive care**[Aggarwalet al, 2001].**Neonatal sepsis is defined as a clinical syndrome in an infant 28 days of life or younger, manifested by systemic signs of infection and isolation of a bacterial pathogen from the bloodstream and can be divided in two main classes **[M. S. Edwards and C. J. Baker et al, 2004]**.**Early onset sepsis**:usually presents within the first 72 hours of life.The source of infection is generally the maternal genital tract. Clinically, neonates usually present with respiratory distress and pneumonia. The main organism is group B streptococci (GBS)**.** **Late onset sepsis**: Late onset sepsis usually presents after 72 hours of age. The source of infection is either nosocomial or community-acquired and neonates usually present with septicemia, pneumonia or meningitis**.** Diagnosis and management of sepsis is difficult due to nonspecific signs and symptoms. In addition, laboratory diagnosis is time consuming. At the same time, increased multidrug resistant organisms make the treatment options fewer and the effective treatment is delayed **[S. J. Patel and L. Saiman et al, 2010].**Neonatal sepsis is caused by Gram-positive and Gram negative bacteria and Candida **[D. S. JumahandM. K. Hassan et al, 2007].** The diversity of organisms causing sepsis varies from region to another and changes over time even in the same place **[S. Shrestha, N.Adhikari et al, 2010]** this is attributed to the changing pattern of antibiotic use and changes in lifestyle.Blood culture is the gold standard for the diagnosis of septicemia and should be done in all cases of suspected sepsis prior to starting antibiotics. Positive blood culture and sensitivity of the isolate is the best guide to antimicrobial therapy.All newborns suspected to have neonatal sepsis should have a septic screen(total leukocyte count, absolute neutrophil count, immature to total neutrophil ratio, erythrocyte sedimentation rate and C reactive protein).Other investigations include urine culture that has been recommended for all cases of late onset sepsis,CSF examination and culture for suspected cases of meningitis and radiological studies as X-ray chest and abdomen and CT head scan should be done in all patients diagnosed to have meningitis.Sepsis related mortality is largely preventable with rational antimicrobial therapy with aggressive supportive care. Antibiotics once started should be modified according to the culture sensitivity reports.

2-Patients and Methods

I)Study design: This study was prospectively conducted at Sohag university hospital over a period of 18 months between October 2015 and April 2017. During the study period, all admitted neonates with clinical signs and symptoms of sepsis at the time of admission or who developed sepsis during their hospital stay were assessed using EGNN (Egyptian Neonatal Network) sepsis screening tool and included in this study.Sepsis was evaluatedclinically (poor reflexes, lethargy, respiratory distress, apnea, bradycardia, convulsions, abdominal distension and bleeding) and laboratory.

II) Collection and processing of specimens: Under complete aseptic conditions blood samples collected from the neonates with suspected sepsis for CRP, ESR, CBC and blood cultures and

sent to our clinical microbiology laboratory for cultivation and subsequent processing.

III)Preservation of clinical isolates (Collee et al., 1996): Once the organism had been isolated, it was purified and preserved on slants of nutrient agar (for short period preservation), in 25% glycerol stocks at -80°C to maintain its viability, purity and genetic characters over a long term.

IV)Identification of the clinical isolates: Isolates obtained were identified according to Bergey's manual of Bacteriology **(Holt et al., 1994)**, using; Gram staining, colony characteristics and hemolytic activity on blood agar plates for Gram positive isolates.VITEC 2 Compact 15 identification kits used to confirm the identification of the isolates.Candida isolates were confirmed by growth on sabouraud media.

V)Determination of antibiotic susceptibility pattern of isolated organisms (Bauer et al., 1966): Antimicrobial susceptibility testing of all bacterial isolates was performed by the Kirby-Bauer disc diffusion method on Muller-Hinton agar(Oxoid). Multidrug resistant bacteria (MDR) were defined by resistance to three or more antimicrobial classes.

VI)Statistical analysis: Summary of measures was reported as mean ± standard deviation (SD) for quantitative variables and percentages for categorical variables. The differences in distribution were evaluated using the chi-square test for categorical variables. P value ≤0.05 was considered statistically significant.

Results

1-Base line demographic and clinicaldata (table 1): all cases presented with late onset sepsis with higher females gender, most of case presented after C.S delivery especiallylow or very low birth weight.Most common presentations were poor activities with hypotonia, pneumonia and respiratory infections, temperature instability, hematologic symptoms and neonatal jaundice.

Table (1) Maternal and Neonatal data

Data	Category	Number	Percentage %
Sepsis onset	late onset	75	100
	early onset	0	0
Sex	Male	33	44
	Female	42	56
Delivery mode	Vaginal	25	33.3
	C.S	50	66.7
Delivery place	Home	3	4
	Hospital	42	56
	Private clinic	30	40
Birth weight	Normal(>or=2500)	25	33.3
	LBW(1501-2500)	35	46.7
	VLBW(1001-1500)	15	20
Gestational age	Term(>or=37w)	40	53.3
	Preterm(<or=33w)	25	33.4
	Late preterm(34-36w)	10	13.3

2-Biochemical, hematological and bacteriological data (tables 2, 3):CRP was positive in all cases, 48% of cases presented with leucocytosis while12% presented with leucopenia.40% of cases presented with neutrophilia while20 % presented with neutropenia.53% of cases presented withthrombocytopenia.45% of isolates were Gram +ve organisms with 55% Gram -veorganisms.96%of cases showed positive culture on blood agar, 53.3% on Mackonkey agar with no growth on chocolate agar.

Table (2) Gram staining

Gram stain	Number	Percentage %
Positive	34	45.3
Negative	41	54.7
Total	75	100

Table (3) Subculture of the isolates on Blood agar, MacConkey agar and Chocolate agar.

Positive culture	Number of cases	Percentage %
1-Blood agar	72	96
2-Mackonkey agar	40	53.3
3-chocolate agar	no	0

3-Isolated organisms (tables 4 and 5): Main isolated organisms wereklepseillapneumonaefollowed by staph. haemolyticus and staph. epidermidis.Klebseilla organism encountered mainly in hospital deliveries specially LBW and preterm's presented with pneumonia and respiratory distress while fatal meningitis and convulsions mainly caused by staphylococcus species.

Table (4) Microbiological profile found in positive blood cultures from suspected neonates.

Isolated organisms	Number of cases	Percentage %
Klepseillapneumonae	34	45.3
staphylococcus aureus	6	8
staphylococcus epidermidis	10	13.4
staphylococcus haemolyticus	13	17.3
pseudomonas aeruginosa	1	1.3
Staphylococcushominis	4	5.3
E.coli	7	9.4
Total	75	100

Table (5) Relation between demographic and clinical data with isolated organism.

Variable	Subgroups	Isolated organisms							
		Klebseilla	S. aureus	S. epidermidis	S. Haemolyticus	Pseud.	S. hominis	E. coli	T
Delivery place	Home	2	0	0	1	0	0	0	3
	Hospital	20	3	6	8	0	2	3	42
	Private	12	3	4	4	1	2	4	30
Delivery mode	Vaginal	14	0	5	6	0	0	0	25
	C.S	20	6	5	7	1	4	7	50
Birth weight	Normal	12	0	3	7	0	3	0	25
	LBW	21	1	3	6	1	1	2	35
	VLBW	1	5	4	0	0	0	5	15
Gestational age	Term	15	6	6	6	1	2	3	39
	Preterm	16	0	3	2	0	2	2	25
	Late preterm	3	0	1	5	0	0	2	11
Respiratory distress		16	0	3	2	0	3	1	25
Pneumonia		9	0	6	0	0	0	1	16
Convulsions		0	0	0	5	0	0	0	5
Meningitis		0	0	1	2	0	0	0	3
Shock		2	2	0	1	0	0	0	5
Haematologic symptoms		7	2	3	3	0	0	0	15
Neonatal jaundice		7	2	2	3	0	0	1	15
Hypotonia		28	5	9	10	1	4	3	60

4-Antibiotic sensitivity testing (tables 6-8, figure 1): Klebseilla isolates showed high sensitivity for aminoglycosides and quinolones antibiotics while resistance to penicillin's group.Staphylococcus isolates showed resistance to penicillin's and aminoglycosides while

sensitive to quinolones and nitrofurantions.E.coli and pseudomonas species showed moderate sensitivity to 3rd generation cephalosporins, aminoglycosides, quinolones and nitrofurantoins while resistance to classic penicillin's.

Table (6) antimicrobial agents sensitivity among bacterial isolates from the suspected neonates.

Antibiotic	Sensitive		Intermediate		Resistant		Not done	
	Number of cases	Percentage	Number of cases	Percentage	Number of cases	Percentage	Number of cases	Percentage
Ampicillin	-	-	-	-	70	93.3	5	6.7
Oxacillin	-	-	-	-	73	97.4	2	2.6
Amoxycillin| Clavulonic	-	-	-	-	74	98.7	1	1.3
Cefoxitin	6	8	-	-	69	92	-	-
Cefotaxime	-	-	3	4	67	89.3	5	6.7
Ceftriaxone	5	6.7	1	1.3	69	92	-	-
Ceftazidime	5	6.7	1	1.3	69	92	-	-
Imipenem	-	-	-	-	2	2.7	73	97.3
Tobramycin	5	6.7	2	2.6	63	84	5	6.7
Gentamycin	40	53.3	-	-	35	46.7	-	-
Amikacin	40	53.3	-	-	35	46.7	-	-
Erythromycin	6	8	-	-	61	81.3	8	10.7
Azithromycin	-	-	-	-	43	57.3	32	42.7
Ciprofloxacin	51	68	12	16	7	9.3	5	6.7
Norfloxacin	15	20	41	54.7	14	18.6	5	6.7
Levofloxacin	54	72	16	21.3	5	6.7	-	-
Nitrofurantoin	72	96	-	-	3	4	-	-
TMSZ	4	5.3	-	-	71	94.7	-	-

Table (7) Comparative Resistances of isolated organisms to different antimicrobial agents.

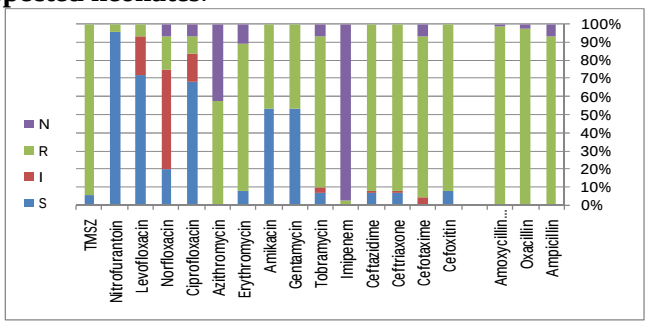
Antibiotic	S								
		Klebseilla	S.aureus	S.epidermidis	S.haemolyticus	Pseudomonas	S.hominis	E.coli	T
Ampicillin	R N	33 1	6 0	8 2	13 0	1 0	4 0	5 2	70 5
Oxacillin	R N	34 0	6 0	10 0	13 0	1 0	4 0	5 2	73 2
Amox.clavulanic	R N	34 0	6 0	10 0	13 0	0 1	4 0	7 0	74 1
Cefoxitin	S R	0 34	0 6	0 10	0 13	0 1	0 4	6 1	6 69
Cefotaxime	I R N	0 34 0	0 6 0	0 10 0	0 13 0	0 0 1	0 4 0	3 0 4	3 67 5
Ceftriaxone	S I R	0 0 34	0 0 6	0 0 10	0 0 13	0 1 0	0 0 4	5 0 2	5 1 69
Ceftazidime	 R	0 34	0 6	0 10	0 13	0 0	0 4	5 2	6 69
Imipenem	R N	0 34	1 5	0 10	0 13	0 1	0 4	1 6	2 73
Tobramycin	S I R N	0 0 34 0	0 0 6 0	0 0 6 4	0 0 12 1	0 0 1 0	0 0 4 0	5 2 0 0	5 2 63 5
Gentamycin	S R	34 0	0 6	0 10	0 13	0 1	0 4	6 1	40 35
Amikacin	S R	32 2	0 6	0 10	0 13	1 0	0 4	7 0	40 35

Table (8) Comparative Resistances of isolated organisms to different antimicrobial agents.

Erythromycin	**S**	**0**	**6**	**0**	**0**	**0**	**0**	**0**	**6**
	R	**34**	**0**	**10**	**13**	**0**	**4**	**0**	**61**
	N	**0**	**0**	**0**	**0**	**1**	**0**	**7**	**8**
Azithromycin	**R**	**20**	**0**	**6**	**13**	**0**	**4**	**0**	**43**
	N	**14**	**6**	**4**	**0**	**1**	**0**	**7**	**32**
Ciprofloxacin	**S**	**34**	**6**	**4**	**0**	**0**	**4**	**3**	**51**
	I	**0**	**0**	**1**	**10**	**1**	**0**	**0**	**12**
	R	**0**	**0**	**0**	**3**	**0**	**0**	**4**	**7**
	N	**0**	**0**	**5**	**0**	**0**	**0**	**0**	**5**
Norfloxacin	**S**	**7**	**1**	**3**	**0**	**0**	**4**	**0**	**15**
	I	**27**	**5**	**7**	**2**	**0**	**0**	**0**	**41**
	R	**0**	**0**	**0**	**10**	**0**	**0**	**4**	**14**
	N	**0**	**0**	**0**	**1**	**1**	**0**	**3**	**5**
Levofloxacin	**S**	**33**	**6**	**5**	**4**	**1**	**0**	**5**	**54**
	I	**1**	**0**	**2**	**9**	**0**	**4**	**0**	**16**
	R	**0**	**0**	**3**	**0**	**0**	**0**	**2**	**5**
Nitrofurantoin	**S**	**34**	**6**	**10**	**13**	**0**	**3**	**6**	**72**
	R	**0**	**0**	**0**	**0**	**1**	**1**	**1**	**3**
TMSZ	**S**	**0**	**4**	**0**	**0**	**0**	**0**	**0**	**4**
	R	**34**	**2**	**10**	**13**	**1**	**4**	**7**	**71**

S=sensitive. R=resistant. I=intermediate. N=not done. T=total

Figure1: Percentage of resistance to the tested antimicrobial agents among the bacterial isolates from the suspected neonates.



Discussion:

The clinical signs and symptoms of neonatal sepsis are non-specific, making early diagnosis difficult. Blood culture is still the gold standard in definitive diagnosis of neonatal sepsis.In our studyall studied neonates presented with late onset sepsis with higher incidence in infants born via CS especially with low and very low birth weight (66% with CS, 66.7% LBW and VLBW). This finding is similar with other previous studies as **(EmanShehab El-Din et al.,2015; Utomo., 2010; Afsharpaiman et al., 2012; Gandhi et al., 2013)**.As in the study of **[Utomo et al.,(2010)]**, in Indonesia (Surabaya), it was reported that infant delivered via CS have a1.89 times higher risk to develop sepsis than non caesarean delivery and in another study **[EmanShehab El-Din et al.2015]** it was 69.7% of neonates with CS delivery and LBW and VLB.The incidence of neonatal sepsis was predominantly due gram negative bacteria (56%) mainly Klepseillapneumonae (45.3%) may be due to extensive use of invasive devices for caring the immunologically immature infants especially preterm and LBW, followed by staphylococcus haemolyticus (17.3%) and staphylococcus epidermidis (13.4%).The predominance of Klebsiella among the causative Gram negative pathogens was also found in other studies from Egypt like **(El Badawy et al., 2005; Fahmey., 2013)**and other different countries **(Kapoor et al., 2005, Macharashvili et**

al., 2009;Chiabi et al., 2011; Kohli-Kochhar et al., 2011; Leal et al., 2012; Li et al., 2013).In our studyKlebseilla isolates showed high sensitivity for aminoglycosides and quinolones antibiotics while resistance to penicillin's group, Staphylococcus isolates showed resistance to penicillin's and aminoglycosides mostly due misuse of antibiotics in hospitals that leads to this significant resistant while sensitive to quinolones and rarely used antibiotics like nitrofurantions, E.coli and pseudomonas species showed moderate sensitivity to 3rd generation cephalosporins, aminoglycosides, quinolones and nitrofurantoins while resistance to classic penicillin's, this data are in line with study of **[Kohli-Kochhar et al., (2011)].**

Conclusion:

All studied neonates in our study presented with late onset sepsis with females slightly higher than males (54% females-44% males).The incidence of sepsis was higher in infants born via CS especially with low and very low birth weightwithKlebseilla organism encountered as main organism and presented with pneumonia and respiratory distress while fatal meningitis and convulsions mainly caused by staphylococcus species**.**The incidence of neonatal sepsis was predominantly due gram negative bacteria mainly Klepseillapneumonae may be due to extensive use of invasive devices for caring the immunologically immature infants especially preterm and LBW followed by staphylococcus haemolyticusand staphylococcus epidermidis.Klebseilla isolates showed high sensitivity for aminoglycosides and quinolones antibiotics with resistance to penicillin's group, Staphylococcus isolates showed resistance to penicillin's and aminoglycosides while sensitive to quinolones and nitrofurantions, E.coli and pseudomonas species showed moderate sensitivity to 3rd generation , aminoglycosides, quinolones and nitrofurantoins while resistance to classic penicillin's.

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