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ORIGINAL ARTICLE

Developing A Protocol For Empirical Antibiotics For Neonatal Sepsis Based On Data On Antibiotic Sensitivity Patterns At Two Tertiary Neonatal Units In Southern India

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KSA assisted in collection and analysis of data; KKD is the guarantor and was responsible for the conceiving, planning and executing the study, and preparation of manuscript

ABSTRACT

Sepsis continues to be a major challenge in neonatal care. The choice of first –line antibiotics to be commenced in at-risk neonates has always been a matter of debate.

Objective: To compare the bacteriological profiles of isolates from blood cultures at two neonatal centers situated in different states of India, and evaluate if a common 'first-line combination' of antibiotics could be recommended for infants at-risk for sepsis.

Method: Isolates obtained from neonatal blood culture done at the Kasturba Medical College, Manipal, Karnataka (Center A) and the Malankara Orthodox Syrian Church Medical College, Kochi, Kerala (Center B) were retrospectively analyzed. The sensitivity of common antibiotics and their combinations was analyzed in relation to the bacteriological profile and age of onset of sepsis (Early or late).

Results : Six ninety seven isolates from 3077 samples of blood cultures done in at-risk neonates were retrospectively evaluated. Five twenty nine isolates were obtained from Center A and 168 from Center B. Coagulase negative staphylococcus (CONS) constituted the largest group (37.6%) of these isolates. Klebsiella species (18.5%), Pseudomonas (14.1 %), Acinetobacter sp. (7 %), Enterobacter sp. (4.9 %) were the other common isolates. The combination of Ampicillin + Amikacin covered 49% isolates, followed by Ciprofloxacin + Gentamicin (46.4%), Ciprofloxacin + Amikacin (44%) and Ampicillin + Gentamicin (38.6%). The types of isolates and the sensitivity pattern of isolates to combination antibiotics was found to be similar at both the centers ($r = 0.81$). Addition of a 'third' antibiotic Cefotaxime to the combination of Ampicillin + Amikacin did not reveal any significantly increase in the number of isolates covered. The antibiotic sensitivity patterns were similar among EOS and LOS and correlated at $r= 0.9$ ($p<0.01$) for individual antibiotics and at $r = 0.97$ ($p < 0.01$) for combination antibiotics.

Conclusion : The combination of Ampicillin + Amikacin , covers the maximum numbers of isolates and could be the best first-line antibiotics in neonatal sepsis. Addition of more antibiotics does not necessarily result in wider coverage of isolates. The initial combination of antibiotics could be the same for EOS and LOS. Blood cultures are mandatory in all neonatal sepsis for seeking specific sensitivity patterns and accordingly modifying the antibiotic therapy.

Key Words: Neonatal Sepsis, First-line antibiotics.

Key Message

* A combination of a penicillin and an aminoglycoside – Ampicillin and Amikacin is a satisfactory combination of antibiotics to commence in all infants suspected or presenting with features of sepsis while awaiting blood culture reports.
* Blood culture is a mandatory investigation in the treatment of neonatal sepsis.

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Introduction

Infection, till date, continues to be a bugbear in the management of neonates. Commencing antibiotics in at-risk infants has become the norm of neonatal intensive care. Despite the availability of rapid methods of diagnosis and identification, the choice of the primary antibiotic continues to be based on recommendations of literature. The present study was undertaken to determine the 'first line antibiotics' that would be optimal to commence in at- risk neonate while awaiting the blood cultures and sensitivity report. The authors postulate that obtaining data from two hospitals separated geographically over 500 km, in different states, could provide comparative information that could facilitate a consensus in choosing the 'first-line' antibiotics in neonatal sepsis.

Materials And Methods

Isolates obtained from neonatal blood culture done over a 4-year period from January 1999 to December 2002 at the Kasturba Medical College, Manipal, Karnataka (Center A) and over an 18 months period, from March 2004 to August 2005, at the Malankara Orthodox Syrian Church Medical College, Kochi, Kerala (Center B) were retrospectively analyzed. The indications for blood cultures were the same at both centers. Cultures were done for evaluating at risk neonates and in those infants clinically suspected to have sepsis. The age of presentation, identity of isolates, frequency and sensitivity to commonly used antibiotics were evaluated.

The attempt to search for an ideal combination to cover the largest cluster of isolates was performed by evaluating the sensitivity of isolates to any one of the antibiotics of the selected combination. The profile and sensitivity of isolates were also analyzed separately for both the centers, and the coefficient of correlation determined.

Isolates obtained in blood cultures of infants with in 72 hours of life was considered "Early Onset Sepsis" (EOS) and those beyond 72 hours considered as "Late Onset Sepsis" (LOS). Sensitivity pattern of isolates based on the 'onset of sepsis' was also evaluated. The principal investigator was the same and was head of the neonatal services at both the centers during the study period. Relevant statistical analysis was done using the SPSS version 7.5 statistical package.

Results

Three thousand seventy seven samples of blood cultures were evaluated [Table/Fig 1].Two thousand five hundred forty five of these were from Center A and 532 were from Center B. Isolates were reported in 697 (22.7%). Coagulase negative staphylococcus (CONS) constituted the largest group (37.6%) of these isolate. This was followed by Klebsiella species (18.5%), Pseudomonas (14.1 %), Acinetobacter sp.(7 %), Enterobacter sp. (4.9 %) and other bacteria in varying percentages. The isolates were similar at both the centers though they varied in their frequency of occurrence [Table/Fig 1]. While CONS was the most common isolate at both centers, Enterobacter sp. and Acinetobacter sp. were more common than Klebsiella at Center B.

Contaminants, which included aerobic spore bearing bacilli constituted 6% (42/697) of the total isolates, and were excluded from further analysis [Table/Fig 1].Six hundred fifty five isolates were therefore evaluated for sensitivity

to commonly used antibiotics. Five hundred twenty of these were from Center A and 135 from Center B.

(Table/Fig 1) Study Characteristics

Isolate	Counts (percentage)			Sensitive to common antibiotics , n			Resistant to common antibiotics, n		
	Combined N = 697 (%)	Center A n=529 (%)	Center B n=168 (%)	Combined	Center A	Center B	Combined	Center A	Center B
Acinetobacter	49 (7)	32(6)	17(11)	34	19	15	15	13	2
α hem strepto	10 (1.4)	2(0.3)	8(4.8)	8	1	7	2	1	1
β hem Strepto	2 (0.3)	2(0.3)	0	1	1		1	1	0
Candida	6 (0.9)	1(0.15)	5(3.2)				6	1	5
Citrobacter	14 (2)	12(2.2)	2 (1.4)	12	10	2	2	2	
Coag pos staph	32 (4.6)	30(5.6)	2(1.4)	20	18	2	12	12	
Coag neg Staph	262 (37.6)	215(40.6)	47(28)	186	144	42	76	71	5
Ecoli	10 (1.4)	5(0.9)	5(3)	6	2	4	4	3	1
Enterobacter	34 (4.9)	9(1.7)	25	26	7	19	8	2	6
Enterococci	8 (1.1)	8(1.5)	0	5	5		3	3	0
Klebsiella	129 (18.5)	112(21.2)	17(10.1)	74	61	13	55	51	4
Proteus	1(0.1)	1(0.15)	0				1	1	0
Pseudomonas	98 (14.1)	91(17.2)	7(4.2)	63	58	5	35	33	2
Aerobic spore + Contaminants	42(6)	9(1.6)	33(19.6)						
Total Isolates	697	529	168						
No isolates	2380	2016	364						
Total sample	3077	2545	532						
Isolates evaluated for sensitivity (Excl.contaminants)	**655**	520	135	**435**	326	109	**220**	194	26

Study period: Center A – 4 years, Center B - 18 months.

The antibiotics sensitivity of individual isolates was evaluated [Table/Fig 2]. Gram negative organisms like Enterobacter, Pseudomonas and Klebsiella, were found to be more sensitive to Amikacin. Sensitivity to Ciprofloxacin was seen among both gram negative and gram positive bacteria. The antibiotics sensitivity pattern of identical species of bacteria was found to be different at the two centers [Table/Fig 2]. The correlation for antibiotics sensitivity between the two centers was observed to be best for Enterobacter sp. and (r = 0.8, p =0.05) least for COPS (r =0.04, p = 0.9).

(Table/Fig 2) Antimicrobial Sensistivity Of Individual Types Of Bacteria To Common Antibiotics Comparison Between Center A & Center B (In %)

	N	Amik	Ampi	Cefotax	Cefurox	Ceftazid	Ciprofl	Genta	Penicil	Vanco	Netil	Cotrimox.
Isolate	Cen.A											
Cor (p)	*Cen.B*											
Corr:0.7	32	40.6	12.5	18.8	6.2	0	28.1	25	0	6.2	34.3	21.8
(p= 0.02)	*17*	*35.2*	*5.8*	*17.6*	*11.8*	*5.8*	*70.5*	*47*	*17.6*	*0*	*41.1*	*58.8*
Acineto												
α,h strep	2	0	0	0	0	0	0	50	0	50	0	0
corr: 0.3	*8*	*0*	*75*	*0*	*0*	*0*	*0*	*37.5*	*12.5*	*12.5*	*0*	*0*
p = 0.44												
Citro bact	12	16.7	16.7	25	16.7	0	25	50	0	8.4	58	8.4
Corr=0.3	*2*	*100*	*0*	*50*	*0*	*0*	*50*	*0*	*50*	*0*	*100*	*50*
P = 0.37												
COPS	30	40	23.3	23.3	13.3	0	6.7	53.3	6.7	40	36.7	13.3
Corr;0.04	*2*	*0*	*50*	*0*	*0*	*0*	*0*	*50*	*50*	*0*	*0*	*50*
P = 0.9												
CONS	215	40	32.5	30.6	27.4	1.3	22.3	47.9	4.6	26.5	32	18.6
Corr:0.16	*47*	*4.2*	*27.7*	*2.1*	*0*	*0*	*2.1*	*51.1*	*21*	*2.1*	*2.1*	*61.7*
P= 0.63												
E.Coli	5	40	0	40	20	20	20	20	0	0	20	0
Corr:0.1	*5*	*20*	*40*	*20*	*20*	*0*	*0*	*40*	*0*	*0*	*20*	*20*
P= 0.74												
Enterobact	9	66.7	11.1	0	22.2	0	33.3	11.1	0	0	22.2	11.1
Corr:0.8	*25*	*64*	*0*	*4*	*4*	*0*	*16*	*8*	*0*	*0*	*48*	*8*
P = 0.05												
Klebsiella	112	40.1	1.8	22.3	8	0.9	29.4	18.7	0	0.9	21.4	21.4
Corr:0.6	*17*	*23.5*	*5.9*	*0*	*0*	*0*	*29.4*	*23.6*	*0*	*0*	*23.5*	*52.9*
P = 0.04												
Pseudomon	91	47.2	9.8	25.2	12	1	29.6	38.4	1	2.1	35.1	23
Corr:0.6	*7*	*57*	*0*	*14.3*	*0*	*28.5*	*42.9*	*14.3*	*14.3*	*0*	*42.9*	*0*
P = 0.04												

Individual antibiotics were then evaluated for their 'antimicrobial cover' against the organisms isolated [Table/Fig 3]. The largest clusters of isolates were sensitive to Aminoglycosides --. Amikacin (37.7%) followed by Gentamicin (36.6%) and Netilmycin (28.9%). The sensitivity of isolates to aminoglycosides was followed by Ciprofloxacin (23.8%), Cotrimoxozole (23.5%), Cefotaxime (22%) and Ampicillin (18.5%). Comparison of the 'antimicrobial cover' of individual antibiotics at Center A and Center B [Table/Fig 3] were not identical and correlated at r = 0.57 (p = 0.07).

(Table/Fig 3)Antibiotic Sensitivity Of Isolate Clusters To Common Drugs

	Total n = 655		Center A N = 520		Center B N = 135	
Antibiotic	**Sensitive N**	**% of total isolates**	n	%	n	%
Amikacin	**247**	**37.7**	212	40.8	35	25.9
Gentamicin	**240**	**36.6**	195	37.5	45	33.3
Netilmycin	**189**	**28.9**	159	30.6	30	22.2
Ciprofloxacin	**156**	**23.8**	130	25	26	19.3
Cotrimoxozole	**154**	**23.5**	101	19.4	53	39.3
Cefotaxime	**144**	**22**	136	26.2	8	5.9
Ampicillin	**121**	**18.5**	97	18.7	24	17.8
Cefuroxime	**97**	**14.8**	93	17.9	4	3
Vancomycin	**80**	**12.8**	78	15	2	1.5
Penicillin	**30**	**4.6**	13	2.5	17	12.6
Ceftazidime	**9**	**1.4**	6	1.2	3	2.2

Coefficient of correlation Center A vs Center B , r = 0.57, p = 0.07

Antibiotic combinations commonly used in clinical practice, were assessed for the widest coverage against the isolates [Table/Fig 4]. Eg. The combination of Ampicillin and Amikacin was evaluated to see if the isolates were sensitive to either Ampicillin OR Amikacin [Table/Fig 4]. Ampicillin + Amikacin covered the largest cluster of bacteria (49%). This was followed by Ciprofloxacin + Gentamicin (46.4%), Ciprofloxacin + Amikacin (44%) and Ampicillin + Gentamicin (38.6%). The three drug combination of Cefotaxime + Ampicillin +Amikacin covered 50.5% while Cefotaxime+Ampicillin+Gentamicin covered 44.9% of the isolates. The numbers of isolates sensitive to the combination Ampicillin + Amikacin was compared to the combinations of other antibiotics and chi square test applied. The numbers of isolates sensitive to Ampicillin + Amikacin was significantly more than Ampicillin + Gentamicin (Chi square = 14.3, p = 0.002), Cefotaxime + amikacin (chi square = 8.7, p = 0.003), and Cefotaxime + Gentamicin (chi square = 3.98, p = 0.046). However, sensitivity of combination of Ampicillin + Amikacin was not significantly different from the combination of Ciprofloxacin + Gentamicin (Chi square = 0.88, p = 0.34). Though a greater percentage of isolates were sensitive to the combination Cefotaxime + Gentamicin than Cefotaxime+Amikacin, the difference was not statistically significant (chi square =0.9, p=0.3). The differential evaluation of the centers showed that while in center A coverage provided by Ampicillin + Amikacin (51.3%) was followed by Ciprofloxacin + Gentamicin (47.7%), in Center B the combination of Ciprofloxacin + Gentamicin (44.4%) covered a few more isolates than Ampicillin + Amikacin (43%). The percentage of isolates sensitive to combination of antibiotics were similar at both the centers and correlated at r =0.8 (p = 0.008) [Table/Fig 4].

Three hundred eighty nine (59%) isolates were of EOS and 266 (41%) were of LOS. The antibiotic sensitivity patterns of the isolate clusters of EOS and LOS were compared. The sensitivity patterns correlated well for individual antibiotics (r = 0.9, p =<0.01) [Table/Fig 5], as well as for the common combinations of antibiotics (r = 0.97, p = <0.01) (Table 6).33.6% (220/655) of the isolates were resistant to all the commonly plated antibiotics. [Table/Fig 1]. Multi drug resistance was most common amongst Klebsiella, (43%), Pseudomonas (36%) Acinetobacter (30%) and CONS (29%). One hundred twenty five of the 389 isolates of EOS and 87 of the 266 of LOS were resistant to the commonly used antibiotics and their combination[Table/Fig 6]. There was no higher risk of resistance in LOS. (Relative Risk= 1.01 (0.91 – 1.12) at 95 % Confidence limits, p= 0.8, ns)

(Table/Fig 4) Sensitivity Of Isolate Clusters To Common Combinations Of Drugs

	Total N = 655		Center A, n =520		Center B, n = 135	
Drug combination	**Numbers of Isolates sensitive**	%	Isolates sensitive	%	Isolates sensitive	%
Ampicillin + Gentamicin	253	**38.6**	203	**39**	50	**37**
Ampicillin + Amikacin	321	**49**	267	**51.3**	58	**43**
Ampicillin + Cefotaxime	268	**40.9**	184	**35.4**	30	**22**
Cefotaxime + Gentamicin	285	**43.5**	242	**46.5**	48	**35.6**
Cefotaxime + Amikacin	268	**40.9**	233	**44.8**	39	**28.9**
Cefotaxime + Amikacin + Ampicillin	331	**50.5**	274	**52.7**	61	**45.2**
Cefotaxime + gentamicin + Ampicillin	294	**44.9**	241	**46.3**	53	**39.3**
Ciprofloxacin + Gentamicin	304	**46.4**	248	**47.7**	60	**44.4**
Ciprofloxacin + Amikacin	288	**44**	243	**46.7**	49	**36.3**

Coefficient of correlation Center A vs Center B, r = 0.81 (p = 0.008)

(Table/Fig 5)Comparison Of Isolates Of EOS And LOS For Sensitivity To Drugs

	EOS - 389		LOS N = 266		Total = 655	
Antibiotic	N	%	N	%	N	%
Amikacin	160	**41.1**	87	**32.7**	247	37.7
Gentamicin	156	**40.1**	84	**31.6**	240	36.6
Netilmycin	122	**31.4**	67	**25.2**	189	28.9
Ciprofloxacin	106	**27.2**	50	**18.8**	156	23.8
Cotrimoxozole	85	**21.9**	69	**25.9**	154	23.5
Cefotaxime	103	**26.5**	41	**15.4**	144	22
Ampicillin	79	**20.3**	42	**15.8**	121	18.5
Cefuroxime	68	**23.5**	29	**10.9**	97	14.8
Vancomycin	51	**17.6**	29	**10.9**	80	12.8
Penicillin	16	**4.1**	14	**5.3**	30	4.6
Ceftazidime	5	**1.36**	4	**1.5**	9	1.4

EOS vs LOS coefficient of correlation, r = 0.9 (p =<0.01)

(Table/Fig 6) Comparison Of Isolates Of EOS And LOS For Sensitivity To Common Combinations Of Drugs

Drug combination	EOS N=389	%	LOS N = 266	%	total Isolates sensitive	% (655)
Ampicillin + Gentamicin	161	**41.4**	92	**34.6**	253	38.6
Ampicillin + Amikacin	206	**53**	115	**43.2**	321	49
Ampicillin + Cefotaxime	145	**37.3**	69	**25.9**	268	40.9
Cefotaxime + Gentamicin	189	**48.6**	101	**38**	285	43.5
Cefotaxime + Amikacin	178	**45.8**	94	**35.3**	268	40.9
Cefotaxime + Amikacin + Ampicillin	216	**55.5**	119	**44.7**	331	50.5
Cefotaxime + gentamicin + Ampicillin	190	**48.8**	104	**39.1**	294	44.9
Ciprofloxacin + Gentamicin	200	**51.4**	108	**40.6**	304	46.4
Ciprofloxacin + Amikacin	186	**47.8**	106	**39.8**	288	44

EOS vs LOS, coefficient of correlation, r = 0.97 (p = <0.01)

Discussion

The at–risk approach to neonatal sepsis results in higher cost of blood cultures being done in a large number of infants. As is the recommended practice, antibiotics are commenced as soon as blood is drawn for cultures and the drugs stopped if no organism is isolated. In case the cultures show any isolate, the antibiotics are altered based on the sensitivity pattern for drugs. As the clinical symptoms of sepsis are common to many other neonatal diseases, blood cultures still continue to be the golden standard for confirming sepsis. As seen in the present study, such an approach results in a major number of cultures not yielding any isolates.

The choice of primary antibiotics are based on the preferences of the neonatal center and more studies to clarify this have always been sought[1].The presumptive or 'first-line' antibiotic therapy is aimed at commencing antibiotics that have a reasonable chance of being effective against the isolate, while awaiting specific sensitivity reports. Needless to say, the ideal combination should be effective against 100% of the isolates. The quest for the widest coverage has resulted in neonatal centers preferring to use varied combinations of antibiotics, often based on anecdotal observations. The variations in the bacteriological spectrum of sepsis observed by us at the two centers, supports the observations of other workers[2].

Though gram negative bacterial infections as a group were more common [3]**, C**oagulase Negative Staphylococcus (CONS) was seen to be the commonest bacteria isolated [Table/Fig 1]. The resistance of CONS to multiple drugs including Cloxacillin, reiterates the observations of other workers [4] to the emerging trends of resistance in this common isolate. The observed sensitivity of CONS to aminoglycosides could give some solace. However, its sensitivity to specific aminoglycosides were different at the two centers, with more numbers of CONS at center A being sensitive to Amikacin, while Gentamicin covered more numbers of CONS at Center B. This variation in sensitivity to specific aminoglycosides was observed even amongst CONS isolated from a single center [5]. The emergence of Enterobacter sp. as an important cause for neonatal sepsis [6] was supported by the data from Center B.

Aminoglycosides are usually found to be effective against most of the gram negative infections and a large proportion of staphylococci[7]. According to our study quinolones follow aminoglycosides in their coverage of the numbers of organisms isolated [Table/Fig 2],[Table/Fig 3].Thus, highlighting a major role for these drugs , in the management of infants at risk for sepsis[8], [9].

Over 50% of the Klebsiella, Acinetobacter and Staphylococci isolates were found to be sensitive to Cotrimoxozole [Table/Fig 2]. More isolates were found to be sensitive to this drug at Center B than at Center A. However, the non availability of parenteral preparations, and the risk of its sulpha component displacing bilirubin from albumin binding sites, limits the use of Cotrimoxozole in early neonatal sepsis. The role of Cotrimoxozole could nevertheless be considered when neonates have to be managed at the outback community level, where health care is delivered by the community health workers [10].

The differences in the bacteriological profile are quoted as an important reason by clinicians to

avoid a uniform approach to 'first-line' antibiotic therapy in neonates at-risk of sepsis at various hospitals. The primary objective of the clinician, while awaiting culture and sensitivity reports, is to administer that combination of antibiotics which would cover the widest spectrum of suspected bacteria in neonatal sepsis.

Resistance to Ampicillin and a greater sensitivity to Aminoglycosides have been often reported [11]. The isolates obtained in this study were evaluated for their sensitivity to either or any of the drugs in combination. Implying, that, if a combination therapy was to be implemented, there would be a reasonable chance, of at least one of the drugs in the combination being effective against the isolates. Despite, the limited sensitivity to Ampicillin[Table/Fig 3] the combination of Ampicillin + Amikacin was observed to be sensitive for the largest cluster of isolates [49 %, Table/Fig 4].

Though higher numbers of isolates were sensitive to Cefotaxime than Ampicillin [Table/Fig 3], combining them with Aminoglycosides, yielded varying percentages of sensitivity. The sensitivity being categorized as (Ampicillin + Amikacin) > (Cefotaxime+ Gentamicin) > (Cefotaxime + Amikacin) > (Ampicillin + Gentamicin) . It was observed that despite Amikacin provided a wider coverage than Gentamicin [Table/Fig 3], the combination of 'Cefotaxime + Gentamicin' covered more isolates than 'Cefotaxime + Amikacin'. The difference however was not statistically significant (chi square =0.9, p=0.3). These observations indicate that in the present study, more organisms were sensitive-in-common to the combination of Amikacin and Cefotaxime than to Gentamicin and Cefotaxime. Thus, the overlap in the sensitivity patterns of Cefotaxime and Amikacin narrows the presumptive coverage for this combination. Similarly, the total numbers of isolates sensitive to the combinations of Ampicillin + Amikacin and Ciprofloxacin+ Gentamicin were comparable (p = 0.34, ns).

It was noted that despite the variations in the patterns of bacterial isolates [Table/Fig 1] and varying sensitivity of individual isolates at both the centers [Table/Fig 2], the antimicrobial efficacy of antibiotic combinations [Table/Fig 4] were fairly similar (r=0.8, p = 0.008).It was also noted that adding more number of antibiotics did not significantly increase the coverage eg. Ampicillin +Amikacin +Cefotaxime yielded only 1.5% increase in coverage as compared to Ampicillin + Amikacin (p =0.6, ns). It is, therefore, high time for clinicians to contemplate if the benefit of empirical addition of more antibiotics to the combination is justifiable, since the risk of toxicity would undoubtedly be higher.

We attempted to evaluate, if a uniform antibiotic policy could be advocated despite the differences in bacteria isolated. This presumption was based on the hypothesis that despite their diversity the different types of bacteria isolated could possibly be sensitive to the same antibiotic/combination of antibiotics. It is therefore, reasonable to surmise that the same antibiotic or combination of antibiotics could cover a wide –though not necessarily identical - cluster of bacterial isolates at different neonatal centers. The isolates of Center A and Center B showed a wider variation in their sensitivity, to individual antibiotics than to combinations of antibiotics [r = 0.81, p = 0.008, Table/Fig 4]. Thus reaffirming, that a rational combination of antibiotics could be equally effective at different neonatal centers.

It is often recommended that choice of antibiotics for 'Late Onset Sepsis' and 'Early Onset Sepsis' should be different as the bacteriologic profiles would differ. In our observations however, we noted that the spectrum of antibiotic sensitivity of both EOS and LOS correlated well with each other(r = 0.9, p < 0.01), for single as well as combination antibiotics. Our study did not reveal any higher risk for resistance to commonly used antibiotics from isolates in LOS than EOS. It could therefore be inferred that, the suggested combination of antibiotics could be initiated in all high-risk neonates or those suspected to have sepsis – irrespective of the age of presentation.

Despite its limitations, 'Penicillins + Aminoglycoside' combination continues to be

the optimal drug combination for at –risk infants, while awaiting the specific culture-sensitivity reports. Ampicillin + Amikacin was the most optimal combination in the present study. Ampicillin-sulbactum [12] was not assessed in the study.

Ciprofloxacin and an amino glycoside, was observed to be another promising combination and requires more attention. The poor CSF penetrability of Ciprofloxacin however, limits its value. The fact that nearly 50 % isolates were found to be sensitive to combinations other than Ampicillin + Amikacin , highlights the absolute necessity of obtaining blood cultures in all at risk infants.

Conclusion

This study,therefore concludes that Ampicillin + Amikacin could be a suitable combination as the '1st line antibiotics' in neonatal sepsis, while awaiting blood culture reports. The variations in the bacterial flora of neonatal centers is no indication for substituting the standard 'first line' combination of 'penicillin + aminoglycoside' with more 'exotic' combination in at- risk neonates. A conservative approach while choosing antibiotics is perhaps better than embarking on combinations that include the 'latest' antibiotics for the 'elusive' 100% cover.

Increasing the numbers of antibiotics in any combination need not yield a proportionate increase in the antimicrobial cover. [Table/Fig 4].The high correlation between their antibiotic sensitivity patterns, and the absence of any greater risk for antibiotic resistance in LOS, seems to justify commencing the same combination of drugs, viz. Ampicillin + Amikacin as initial antibiotics in both early and late onset sepsis.

It can never be reiterated enough that blood cultures are mandatory in neonatal sepsis for rationalizing antibiotic therapy. Empirical cocktails of antibiotics based on anecdotal reports or personal preferences should never supersede the meticulous blood culture and sensitivity reports. Larger studies involving more neonatal centers could perhaps be useful in recommending a uniform drug policy in treating neonates who are at-risk for sepsis.

Limitations

Information on baseline characteristics of the patients (gestational age, birth weight, patients on long lines, TPN etc) were not assessed in the study.

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