Misuse of Antimicrobial Agents in Neonatal Units: A Cross-Sectional Survey in Kuwait

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Key Words

Neonatal unit · Nosocomial infection ·
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Abstract

Objective: To evaluate the justification for the use of antimicrobial agents and to verify the possibility of its misuse among inpatient neonates. **Methods:** A cross-sectional 1-day study was conducted. Two questionnaires A and B relating to inpatient neonates were filled by registrars working in the four neonatal units of the main regional hospitals (Maternity, Farwaniya, Adan, and Jahra). The objectives of the study were not revealed to the registrars. **Results:** Of the 119 patients, 57 (48%) were on antimicrobial agents, and the cultures yielded positive in 25/57 (44%). The organisms were reported not to be susceptible to the antimicrobial agents in use in 19/25

(76%) of the cases, but it was continued in 4/19 (21%). Antimicrobial agents were also continued in another 9/32 (28%) despite negative culture results. **Conclusion:** Misuse of antimicrobial agents was homogeneously observed at various levels in all neonatal units. This implies that urgent action should be taken to overcome this problem.

Introduction

Antimicrobial agents are very commonly used in the neonatal units as the clinical signs and symptom of sepsis in these patients can be very nonspecific, to a degree that infection must be considered in virtually all cases of neonatal distress [1]. Also despite advances in various aspects of neonatal medical practices, and the improved overall survival, infections

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remain a serious cause of morbidity and mortality [1–3]. Clinicians' awareness of this problem might have increased the tendency for excessive use of antimicrobial agents, hence almost all critically ill neonates receive antimicrobials during their hospital stay, close to 90% in some reported series [4, 5]. This phenomenon has resulted in increasing resistance of nosocomial pathogens in the neonatal intensive care units all over the world [2–7]. Kuwait has been concerned about the issue of the misuse of antimicrobial agents. In the last two decades there have been several studies to investigate this misuse [8–10]. However, to the best of our knowledge, this matter has not been looked into in the neonatal population. Hence this cross-sectional study was conducted in the neonatal units of the four regional hospitals in Kuwait namely: Maternity, Farwaniya, Adan and Jahra Hospitals, in order to evaluate the appropriateness of the use of antimicrobial agents.

Patients and Methods

A questionnaire 'A' was distributed to the registrars working in the neonatal units of the four regional hospitals. The staff were requested to include information about all neonatal inpatients on one particular day (11th June 1996). The information included was general epidemiological data, birth weight and gestational age, perinatal events and risk factors related to infections. Specific questions were asked about the indications for starting an antimicrobial agent, i.e., if the patient was already started on it on that day. Based on the reported indications the patients were categorized into three groups: (1) suspected sepsis: if the patient had clinical evidence of sepsis; (2) prophylactic: if the patient was undergoing an invasive procedure such as ventilation, catheterization, or was on steroids, and (3) miscellaneous: if the patient did not have 'suspected sepsis' or 'prophylactic' indications. Another questionnaire 'B' was distributed to be filled up after a 3-month period. This included information about results of cultures and susceptibility of isolates from the latest specimens collected before and/or on 11th June 1996 and

the total number and duration of antimicrobials used after the availability of culture and susceptibility results. The aim of the study was not revealed to the doctors involved in collecting and recording the data.

The methods used for collecting blood, culturing organism(s), identification and antimicrobial susceptibility were identical in three units: Farwaniya, Adan and Jahra Hospitals. Samples were collected in Bactec Peds Plus Medium (Becton Dickinson Inc., Cockeysville, Md., USA) and incubated in the Bactec 9240 (Becton Dickinson). Vitek gram-negative identification and gram-positive identification cards (bioMerieux Vitek Inc., Hazelwood, Mo., USA) and analytical profile index strips (bioMerieux, Marcy L'Etoile, France) were used for identification of isolates, and Vitek cards (bioMerieux) were used for antimicrobial susceptibility testing [11, 12]. In the Maternity Hospital isolates were identified by a standard manual and analytical profile index, and the organism susceptibility was determined by the Kirby-Bauer disc diffusion method [11, 12].

Septicemia was diagnosed by a positive blood culture, meningitis by a positive cerebrospinal fluid culture, and pneumonia by clinical and radiological signs plus a positive endotracheal or nasopharyngeal culture. Urinary tract infection was diagnosed by positive urine culture with a single organism at greater than 10⁴ colony-forming units per milliliter.

χ^2 test with Yates' correction was used for analyzing the statistical significance of various data; p value <0.05 was considered as statistically significant.

Results

The population of Kuwait in the 1996 census was 1,753,981 with a crude birth rate of 25.4 per 1,000 population. In 1996, a total of 30,746 live births were delivered in the four regional hospitals included in this study. This accounts for 70% of the total national live births [13].

The study population consisted of 119 inpatients with a mean age of 15.1 days (range 1–116 days), mean birth weight 2,054 g (range 840–4,600 g) and a mean gestational age of 36.4 weeks (range 26–42 weeks). Male:female ratio was 1.078:1. The nationality of parents was: Kuwaiti 70/119 (59%), non-Kuwaiti

Fig. 1. Amp = Ampicillin; Amk = amikacin; Gen = gentamicin; Ctx = cefotaxime; Van = vancomycin; Oth = others.

Arabs 26/119 (22%) and non-Kuwaiti Asians 23/119 (19%). The place of birth by hospital was as follows: Maternity 58/119 (49%), Adan 23/119 (19%), Farwaniya 20/119 (17%) and Jahra 18/119 (15%). The mode of delivery was vaginal route in 77/119 (65%) and cesarean section in 42/119 (35%). Significant birth asphyxia (Apgar score <5 at 5 min) was present in 4/119 cases (3%). Premature rupture of membranes for more than 24 h was found in 13/119 cases (11%).

Out of 119 patients, 57/119 (48%) were receiving antimicrobial agents on the day of the study, but the total number of these used was 146 agents. This was because all the 57 patients were on at least two agents. In fact, 37/57 (65%) patients were on two agents, 13/57 (23%) were on three or four and 7/57 (12%) were on more than four antimicrobial agents. Ampicillin was the most commonly used antimicrobial agent (55/146; 38%), followed by amikacin (44/146; 30%), gentamicin (19/146; 13%), cefotaxime (8/146; 5%), vancomycin (6/146; 4%), and others (14/146; 10%); cloxacillin, metronidazole, ciprofloxacin, amphotericin B, piperacillin, teicoplanin

and imipenem (fig. 1). The indications of starting antimicrobials were: suspected sepsis in 43/57 cases (75%), prophylactic in 13/57 cases (23%) and miscellaneous in 1/57 case (2%).

The analysis of the second questionnaire revealed that out of the 57 patients on antimicrobial agents, 25/57 (44%) were found to have confirmed sepsis based on positive blood culture in 18/57 cases (32%), and other significant cultures in 7/57 cases (12%, table 1). In confirmed sepsis gram-negative bacteria were isolated in 13/25 cases (52%), gram-positive in 8/25 cases (32%) and *Candida albicans* in 4/25 cases (16%). There were 18/25 cases (72%) of septicemia, 2/25 cases (8%) of meningitis, 5/25 cases (20%) of pneumonia, and 1/25 case (4%) of urinary tract infection. There was an overlap in 1 patient who had septicemia and meningitis caused by the same organism (coagulase-negative staphylococcus). The majority of infections were late onset 19/25 cases (76%), but they were homogeneously distributed among different weight groups (table 2). An analysis of the studied risk factors for infection showed that

Table 1. Distribution of cases with confirmed sepsis according to site of infection

Organism	Septicemia	Meningitis	Pneumonia	UTI	Total
<i>Klebsiella pneumoniae</i>	3	0	1	0	4
<i>Pseudomonas aeruginosa</i>	3	0	1	0	4
<i>Enterobacter</i> sp.	2	0	0	0	2
<i>Proteus</i> sp.	1	0	0	0	1
<i>Flavobacterium</i> sp.	1	0	0	0	1
<i>Acinetobacter</i> sp.	1	0	0	0	1
<i>Staphylococcus aureus</i>	1	0	0	0	1
MRSA	1	0	2	0	3
CNS	2 ^a	1 ^a	1	0	3
<i>Streptococcus viridans</i>	1	0	0	0	1
<i>Candida albicans</i>	2	1	0	1	4
Total	18	2	5	1	25

MRSA = Methicillin-resistant *S. aureus*; CNS = coagulase-negative staphylococcus; UTI = urinary tract infection.

^a One patient had septicemia and meningitis.

Table 2. Distribution of positive cultures according to age of onset and birth weight among confirmed cases of sepsis

Organism	Onset ≤ 48 h old		Onset >48 h old		Total
	≤ 1.5 kg	>1.5 kg	≤ 1.5 kg	>1.5 kg	
<i>Klebsiella</i>	2	0	2	0	4
<i>Pseudomonas</i>	1	1	1	1	4
Other gram-negative organisms ¹	0	2	1	2	5
<i>Staphylococcus</i>	0	0	2	5	7
<i>Streptococcus</i>	0	0	0	1	1
<i>Candida</i>	0	0	3	1	4
Total	3	3	9	10	25

¹ See table 1.

only ventilation and umbilical catheterization were significantly associated with confirmed sepsis (table 3).

In 19/25 (76%) of the cases of confirmed sepsis, the antimicrobial agents being used would not have been effective according to the reported susceptibility of the organism

isolated. Resistance was reported to be 100% for gentamicin, 92% for ampicillin, 69% for amikacin and 53% for cefotaxime (fig. 1). In the 19 cases where in vitro resistance was reported, 4/19 cases (21%) were continued on the same ineffective treatment and an additional antimicrobial agent was added. Out of

Table 3. Significance of various risk factors in sepsis

Risk factor	Sepsis (n = 25)	No sepsis (n = 32)	p value
Birth weight, <1,500 g	15	9	n.s.
Gestation, <33 weeks	16	13	n.s.
Male sex	12	21	n.s.
PROM, >24 h	4	1	n.s.
Umbilical catheter	8	2	<0.05
Mechanical ventilation	7	1	<0.01
Intalipid	8	6	n.s.

PROM = Premature rupture of membranes.

the 6 cases with effective empirical therapy, treatment was continued for more than 2 weeks in 4/6 cases (66%) even in the absence of meningitis or any other indication. In 9/32 cases (28%) antimicrobial agents were continued despite negative culture results, presumably on clinical grounds.

Discussion

Resistance to antimicrobial agents is a serious problem in neonatal units all over the world [2–7]. Although the degree of the use of antimicrobials has shown a significant contribution to the emergence of resistant organisms, other factors intrinsic to the organisms themselves and to the critically ill patients may play a role [2, 14, 15]. As the symptomatology for sepsis in neonates is nonspecific, misuse of antimicrobials is much more probable [15–17]. In this cross-sectional study, we found that 57/119 (48%) of inpatient neonates were receiving antimicrobial agents and the yield of positive cultures was 25/57 (44%). This indicates that the decision of the clinicians to start the treatment was appropriate. However, we found that misuse/over-use exists at four different levels: (1) inappropriate choice of the empirical antimicrobials

in 76% as evidenced by the susceptibility of the reported organisms; (2) prolonged use of appropriate antimicrobials in 66% of cases; (3) continuation of inappropriate antimicrobials in 21% of cases regardless of reports on in vitro resistance, and (4) persistent use of antimicrobials despite negative cultures in 28% of cases.

In a clinical situation, almost all sick neonates are started on empirical antimicrobials, usually a penicillin and an aminoglycoside. Ampicillin is usually the chosen penicillin as it covers *Listeria monocytogenes* which is a common isolate in early neonatal infection in Kuwait [18]. This combination should cover most of the vertically transmitted infections. The situation is different when a neonatal patient gets infected in the unit and the choice of antimicrobial agents must cover more serious nosocomial organisms such as *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, coagulase-negative staphylococci, and *C. albicans* infections. In recent studies in adult patients, resistance to cefotaxime was reported in 46% of *K. pneumoniae* and 73% of *P. aeruginosa* [19]. Similar resistance was reported to ceftazidime against a wide variety of gram-negative bacteria [15] and to vancomycin against enterococci [20]. In our study the isolated organisms were reported to be highly

resistant to most of the commonly used antimicrobial agents, namely gentamicin, ampicillin, amikacin and cefotaxime (fig. 1). As most of the infections showed late onset (76%), it might explain the high resistance of the reported organisms. Recent strains of multi-resistant *Escherichia coli* and *K. pneumoniae* producing an extended spectrum of β -lactamase have been reported in Farwaniya Hospital. The strains showed significantly reduced susceptibility to cefotaxime and were resistant to gentamicin and amikacin [2]. Based on this documented resistance and the fact that we are dealing with neonatal patients, the choice of which antimicrobial agent to use is difficult particularly in late-onset infections. This problem could be overcome by setting up policies stating which antimicrobial agents are suitable for a particular unit to match the susceptibility of organisms regularly isolated in the unit.

In this study, we found 27% of the suspected sepsis group and 69% of the prophylactic group were confirmed cases of sepsis. Only mechanical ventilation ($p < 0.01$) and indwelling catheters ($p < 0.05$) were statistically significant factors associated with sepsis. Many studies report other factors such as low birth weight, prematurity, premature rupture membranes and male sex to be significantly associated with sepsis [1–7]. These factors were found to be not statistically significant in our study. Most neonatologists do not recommend prophylactic use of antimicrobial agents in many of these risk factors, but rather start them at the earliest definite indication of sepsis [1, 4, 6, 7, 14–16]. We strongly support this view. Good hand washing before and after all patient contact is reported to be the most important means of preventing nosocomial infections [21]. Hygienic hand disinfection will remove and/or kill most transient organisms [22]. However, awareness of this concept and its practices should be reinforced

on all medical staff involved in patient care in neonatal units.

Although this was a cross-sectional one-day study with many limitations aimed at covering all the problems of neonatal infection and misuse of antimicrobial agents, it has thrown an insight onto some of the points which we should focus on, when trying to overcome these problems. Hence we propose the following recommendation: (1) Each unit must have a local policy for the use of antimicrobial agents in the treatment of early-onset and late-onset (nosocomial) infections based on continuous surveillance of the etiologic agents and their susceptibility patterns. (2) There should be a rigid control on the use of antimicrobials enforced by the senior medical staff. (3) Antimicrobial agents must be stopped as soon as possible, either after negative cultures, or a maximum of 2 weeks in uncomplicated sepsis. (4) Temptation to use antimicrobials despite reported resistance must be discouraged. (5) Compliance with hand hygiene to prevent nosocomial infections should be enforced.

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