Review Article

Incidence and etiology of omphalitis in Pakistan: a community-based cohort study

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Abstract

Introduction: Although omphalitis (umbilical infections) among newborns is common and a major cause of neonatal deaths in developing countries, information on its burden and etiology from community settings is lacking. This study aimed to determine the incidence and etiology of omphalitis in newborns in high neonatal mortality settings in Karachi, Pakistan.
Methodology: Trained community health workers surveyed all new births in three low-income areas from September 2004 to August 2007. Pus samples from the umbilical stumps were obtained from babies with pre-defined signs of illness and subjected to culture and antimicrobial susceptibility testing.
Results: Among 6904 births, 1501 (21.7%) newborns were diagnosed with omphalitis. Of these, 325 (21.6%) were classified as mild, 1042 (69.4%) as moderate, and 134 (8.9%) as severe; 141 (9.3%) were associated with clinical signs of sepsis. The incidence of omphalitis was 217.4/1000 live births; moderate-severe omphalitis 170.3 per 1000 live births; and associated with sepsis 20.4 per 1000 live births. Of 853 infants with purulent umbilical discharge, 64% yielded 583 isolates. The most common pathogens were *Staphylococcus aureus,* of which 291 (95.7%) were methicillin-susceptible *Staphylococcus aureus* (MSSA) and 13 (4.2%) methicillin-resistant *S. aureus* (MRSA); *Streptococcus pyogenes* 105 (18%); Group B beta-hemolytic streptococci 59 (10 %); *Pseudomonas* spp., 52 (8.9 %); *Aeromonas* spp. 19 (3.2%); and *Klebsiella* spp. 12 (2%).
Conclusions: A high burden of omphalitis can be associated with sepsis among newborns in low-income communities in Pakistan. *S. aureus* is the most common pathogen isolated from umbilical pus. Appropriate low-cost prevention strategies need to be implemented.

Introduction

Neonatal infections account for 12% of global child mortality [1]. In developing countries such as Pakistan, inadequate attention to skilled birth attendance has led to half of all child deaths occurring in the neonatal period, with sepsis as one of the major causes of death [1]. Umbilical infections (omphalitis) are common among newborns in developing countries and may predispose to life-threatening neonatal sepsis [2-4]. Incidence rates in newborns in nurseries from developing countries range from 2 per 1000 to 54 per 1000, with figures from Turkey as high as 77 per 1000 live births. Case fatality rates range from 0-15% in these hospitalized. Very few population-based studies on rates of umbilical infection have been reported [5-8]. Predictably, community-based rates for omphalitis are much higher (105 per 1000 live births in Nepal)

due to the co-existence of many risk factors such as the following the high proportion of babies born at home; low rates of peri-partum skilled birth attendants; sub-optimal use of infection control practices during and after birth (hand washing, disinfection of delivery surface and instruments, sterile cord cutting and tie methods); cultural practices involving application of unsafe substances such as cow dung to the cord; and delayed health-care seeking behavior among families [5]. These sub-optimal peri-partum practices are prevalent in South Asia and may predispose to as high if not higher incidence rates of omphalitis in countries such as Pakistan [9,10].

The objective of this study was to determine the incidence and etiology of non-tetanus omphalitis in low-income community settings of Karachi, where neonatal mortality is high and home births

Table 1. Grading of omphalitis on the basis of severity

Mild
Redness extending to umbilical base but < 2 cm of abdominal wall around umbilical stump involved
No associated purulent discharge
Moderate
Redness around umbilical stump < 2 cm with associated purulent discharge, or purulent discharge alone without any redness
Severe
Redness around umbilical stump with > 2cm extension to abdominal wall, and/or swelling around umbilicus
With or without purulent discharge

predominate. We identified the most common causative organisms and their antimicrobial susceptibility patterns in a community cohort, with a secondary objective to observe association between omphalitis and sepsis and establish appropriate management strategies for omphalitis.

Methodology

Study setting

Pakistan is a large developing country with an estimated population of 180 million. The neonatal mortality rate in Pakistan is 54 per 1000 live births, with two-thirds of all births occurring at home [7].

Karachi is Pakistan's largest city with about 18 million people. This study was conducted in three low-income (two peri-urban and one urban) communities in Karachi where newborn and young infant surveillance and care systems were established to conduct studies on clinical signs predictive of serious illness in young infants [8]. The primary source of income in the two peri-urban coastal areas is derived from fishing while in urban areas manual labor and employment in small factories prevail. Family earnings range from minimum wage to lower-middle income, with the majority averaging less than $1.25 per day (World Bank definition of extreme poverty). Baseline demographic data (from demographic surveillance conducted by the Department of Pediatrics and Child Health, Aga Khan University, in study sites) shows that neonatal mortality in the three study sites is 45 per 1000. Most deliveries are conducted at home by traditional (unskilled) birth attendants (TBAs) who have no formal certification or licensure. The TBAs are local women, often illiterate, who provide pregnancy and child birth care based primarily on experience and knowledge acquired informally through the traditions and practices of the communities. In addition, the use

of sterile delivery kits (as an indicator of effective infection control practices) in home deliveries is low (32%) [6,7,9].

Each community's primary health-care needs for children are provided by Aga Khan University (AKU) Department of Pediatrics and run by the Primary Health Care (PHC) center, which is staffed with physicians and community health workers.

The appropriate approval was obtained from the Aga Khan University's Ethical Review Committee.

Study design

Community health workers (CHWs) were trained to detect clinical signs of serious illness in enrolled pregnant women and newborns through periodic household surveillance in the three sites. Newborn visits by CHWs were conducted within 48 hours of birth and after one week, two weeks, and one month of birth. Over 70% of newborns born at home were seen within 48 hours of birth because of strong links established with local TBAs. Newborns with omphalitis or other illnesses were referred to the PHC center where they were evaluated by study physicians.

For CHW training purposes, a standard picture set was developed by the principal investigator that showed various clinical presentations of omphalitis. The diagnosis of omphalitis was made following the criteria indicated in Tables 1 and 2. If redness extending to the base of the umbilical stump or surrounding abdominal wall was present, and/or purulent discharge from the umbilical stump was noted, the patient was diagnosed with omphalitis. These infections were categorized as mild, moderate, or severe according to definitions based on clinical algorithms from prior community-based work (Table 1) [10]. In addition, babies were also examined for systemic signs of sepsis (Table 2).

Table 2. Clinical Definition of Sepsis

Any three of the following:	
1	Respiratory Rate > 60/minute
2	Feeding difficulty/weak suck
3	Fever > 37.5° C (axillary)
4	Temperature < 36.0°C (axillary) and not increasing on warming
5	Lethargic or < normal movement
6	Excessive crying or irritability
7	Weak, abnormal or absent cry
8	Persistent vomiting (last 3 feeds)
9	Abdominal distension
10	Hypoglycemia – blood glucose < 40 mg/dl
11	Presence of skin, eye, or local umbilical infection

Sample collection and specimen processing

Swabs in Amie's medium (Medical Wire and Equipment, Wiltshire, UK) used to culture babies with umbilical purulent discharge were transported to the Aga Khan University Hospital (AKUH) Clinical Microbiology Laboratory within five hours of collection. Swabs were plated directly to locally prepared 5% sheep blood agar, chocolate agar and MacConkey agar plates. After aerobic incubation of MacConkey plates (35 ± 2°C, air) and chocolate and sheep blood agars (5-10% CO_2) for 24 and 48 hours, the results were reported semi-quantitatively as few colonies, moderate growth, or heavy growth of the recovered organism. Gram-negative bacteria were identified by API 20E and API 20NE kits (bioMérieux, Marcy l'Etoile, France) and *S. aureus* was identified by the tube coagulase test. Lancefield groups of streptococci were determined by latex agglutination with appropriate anti-sera using the PathoDx kit (Remel Inc., Thermo Fisher Scientific USA).

All antimicrobial susceptibilities were performed by the Kirby-Bauer disk diffusion method following the guidelines established by the Clinical Laboratory Standards Institute [11]. The D-test to detect the macrolide-lincosamide-streptogramin-B inducible (MLSBi) phenotype was determined for isolates of *S. aureus*, *S. pyogenes*, and *S. agalactiae*.

Blood cultures were collected from 56 of 141 (39.7%) infants with suspected sepsis and omphalitis whose parents provided consent. After skin disinfection with 70% alcohol swabs, blood was collected in a BACTEC Peds Plus/F bottle (Becton Dickinson, Franklin Lakes, NJ, USA) and transported to the Aga Khan University Clinical Microbiology Laboratory for detection in the automated BACTEC 9240 instrument (Becton Dickinson, Franklin Lakes, NJ, USA). When flagged positive by the instrument, the bottles were examined by Gram stain and bacteria were identified by tests mentioned previously for umbilical cultures [12].

Data analysis

Data was analyzed by the Data Management Unit, Department of Pediatrics, Aga Khan University. Incidence rates and confidence intervals were calculated using SPSS16.0 (SPSS, Chicago, IL, USA). The primary outcomes of omphalitis determined from predominantly home-delivered babies in the community were incidence, etiology, and antimicrobial susceptibilities of the common pathogens causing infections.

Results

Incidence

During the study period of September 2004 to August 2007, there were a total of 6904 births in the three surveillance areas, 65% of which were delivered by TBAs. Among the birth cohort, 1501 (21.7%) were diagnosed with omphalitis by the CHWs. Of these, physicians categorized 325 (21.6%) as mild, 1042 (69.4%) as moderate, and 134 (8.9%)

as severe infections. The incidence of omphalitis was 217.4/1000 live births (95% CI = 207.8-227.3); moderate to severe omphalitis, 170.3/1000 live births (95% CI = 160.8-180.3) and the incidence of omphalitis with sepsis was 20.4/1000 live births (141/ 6904) (95% CI = 17.3- 24). With home or clinic-based antimicrobial therapy, case fatality rate for omphalitis alone was 0.15% (2/1360) and for omphalitis with sepsis, it was 0.7% by day 7 (1/141). The overall case fatality observed in this cohort of infants with omphalitis was 3/1501 (0.2 %).

Etiology

Cultures were collected and processed in 675 (79%) from a total of 853 babies with umbilical purulent secretions. Of 675 specimens cultured, 432 (64%) yielded 583 pathogens; 299 (69%) were pure cultures and 133 (30.7%) were polymicrobial. Among the 141 babies with omphalitis and sepsis, 56 (40%) received parental consent to have blood cultures drawn. However, only one blood culture grew *S. aureus* and one was polymicrobial (*Klebsiella pneumoniae*, *E. coli*, and *Enterobacter spp)*.

Bacteria isolated from the umbilical exudate in descending order of frequency were as follows: *S. aureus* (52%); *Streptococcus pyogenes* (Group A beta-hemolytic streptococci) (18%); *Streptococcus agalactiae* (Group B beta-hemolytic streptococci) (10%); *Pseudomonas spp*. (9%); *Aeromonas spp.* (3.2%); and *Klebsiella* spp. (2%). Umbilical cultures obtained from 54 of 141 babies (38%) with omphalitis and sepsis grew pure cultures in 19 and polymicrobial cultures from 13 cases. Gram-negative bacteria were isolated from 17.8% (8/45) of umbilical cultures obtained from patients with omphalitis and sepsis and 17% (99/583) from those with moderate-severe omphalitis irrespective of sepsis.

Antimicrobial susceptibility patterns

Among 304 *S. aureus* isolates, 13 (4.3%) were methicillin-resistant (MRSA), 291 (95.7 %) were methicillin-susceptible (MSSA), 240 (78.9%) were erythromycin- susceptible, 287 (94.4%) were clindamycin-susceptible, and 204 (67.1%) were cotrimoxazole-susceptible. Two percent of all *S. aureus* were D-test positive. From 164 beta-hemolytic streptococci (Group A = 105, Group B = 59), 121 (73.7%) were erythromycin-susceptible (Group A = 77, Group B = 44), and 142 (86.5%) were clindamycin-susceptible (Group A = 91, Group

B = 51). Fifty percent of *S. pyogenes* was D-test positive and all *S. agalactiae* were D-test negative.

Results for commonly isolated Gram-negative bacteria showed 100% susceptibility to gentamicin and amikacin with *Pseudomonas* spp. (n = 52), *Aeromonas* spp. (n = 19), and *E. coli* (n = 9); and 92% with *Klebsiella* spp. (n = 12). Ciprofloxacin susceptibility was 100%, 98%, 91.6% and 89% with *Aeromonas* spp., *Pseudomonas* spp., *Klebsiella* spp. and *E. coli,* respectively. Susceptibility to ceftriaxone was 91.6% with *Klebsiella* spp. and 89% with *E.coli*.

Discussion

The burden of omphalitis in our population was determined to be 217.4/1000 live births, a rate comparable to that of Gadchiroli, rural Maharashtra, India (197/1000 live births) [13]. We provide additional information regarding the etiology and antimicrobial susceptibility patterns of pathogens causing omphalitis in the study patients.

The umbilical cultures obtained from our patients grew predominantly Gram-positive bacteria, in contrast to one hospital-based study from India where Gram-negative bacteria predominated [14]. This may reflect higher colonization rates with Gram-negative bacteria in babies born in hospitals compared to those born at home. Results demonstrated that *S. aureus* and beta-hemolytic streptococci accounted for 80% of all pathogens causing community-acquired omphalitis. The predominance of *S. aureus* suggests the inclusion of an anti-staphylococcal agent (*e.g.*, cloxacillin) in treatment regimens for infants with omphalitis either with or without sepsis. Although an overall low incidence of MRSA (umbilical cultures) from the community was observed, most of the cases were recovered in the latter half of the study period, which may be indicative of a rise in community-acquired MRSA infections.

It is noteworthy that Group B streptococci (GBS) were isolated from 10% of umbilical exudates but none from blood cultures. The low positivity rate of GBS in blood cultures has also been reported in other developing areas (range of 0.22% in East Asia/Pacific to 15% in Africa). A culture positivity rate of 7% in South Asia stems from community surveillance in Karachi, Pakistan, and tertiary center data in Sevagram and Karnataka, India [15]. GBS neonatal sepsis may be under-detected in South Asia due to the inability to obtain blood cultures within the first 48 hours of life when these bloodstream infections most commonly occur. Newborns delivered at home who develop sepsis do not usually

present to medical facilities to obtain blood cultures and hospital-born babies are often treated with antimicrobial agents before obtaining cultures [16]. Among GBS and *S. pyogenes* isolates, resistance to macrolides (approximately 25%) was higher while that to clindamycin (approximately 13%) was similar to hospital cohort data from India (17.6% *S. pyogenes*; 14.3% GBS) [29-30]. Since macrolides are commonly used to treat respiratory infections in Pakistan, the drug resistance may be a consequence of the availability of antibiotics over the counter without the need of a doctor's prescription.

Reassuringly, antimicrobial resistance in enteric Gram-negative bacteria and *Pseudomonas* spp. was found to be quite low. This is in contrast to the high number of extended spectrum beta-lactamase (ESBL) producing *E.coli* and other enteric pathogens reported from urinary tract infections in developing countries [17-24]. Of interest, *Aeromonas* spp., a known enteropathogen causing diarrhoea, was shown to colonize and possibly infect newborn babies in our study. The clinical consequences of this are unknown.

One limitation of this study was the difficulty in distinguishing the routine physiological inflammatory response and redness associated with cord separation from infected umbilical stumps in cases where discharge is not present. Thus some of the 325 cases (22%) classified as mild omphalitis (redness without discharge) may have represented physiological redness only. Thus we may have over-estimated the true burden of omphalitis in this population. However, even if these cases are excluded, the estimated incidence of omphalitis would be 170 cases per 1000 live births. It is highly recommended that standardized and validated diagnostic criteria defining omphalitis should be developed by the World Health Organization to enable accurate recognition and treatment.

This study did not evaluate possible risk factors contributing to the high incidence of omphalitis in the study population, notably low birth weight and inadequate birth attendant and maternal education. As previously reported, omphalitis could result from the practice of applying non sterile products to the umbilical stump, such as mustard or coconut oil, *surma* (antimony or lead containing compound used to line eyelids), soil or *ghee* (home-made unclarified butter), or animal dung. In addition, unsanitary delivery practices, including poor hand washing, unclean delivery surfaces, and unsterile cord cutting and tying are other contributory factors to developing omphalitis [3,5,25]. Simple, cost-effective interventions can be implemented to reduce risks associated with omphalitis [4,5,9]. Although untreated omphalitis is a high mortality condition [2], the overall case fatality rate of omphalitis in our study was low (0.2%, 3/1501). This was most likely a consequence of early recognition through active surveillance and institution of appropriate antimicrobial therapy in a research setting. Reported case fatality rates in hospital cohorts have ranged from 13-19% [14,26]. In a community-based cohort in rural Nepal, the risk of mortality was found to be 46% higher (95% CI: 8-98%) among infants with omphalitis compared with those without [2]. Use of chlorhexidene antiseptic on the umbilical stump for prevention of omphalitis in this trial reduced neonatal mortality by 24% (RR 0.76, 95% CI 0.55-1.04) compared to dry cord care [4]. Implementation of preventive strategies, as well as early and accurate diagnosis, and appropriate therapeutic management for newborns with omphalitis with and without sepsis are urgently needed for developing countries [25,27,28].

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