Antimicrobial Resistance Among Neonatal Pathogens in Developing Countries

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Introduction: Knowledge of antimicrobial resistance and trends in resistance patterns among major pathogens causing infections in young infants (up to 90 days of life) is an important component of developing community-based management strategies. Hospital-based data suggest alarming rates of resistance to ampicillin and gentamicin, the first-line antimicrobial agents recommended by WHO for treatment of serious infections in young infants.

Methods: We searched the literature published since 1990 for studies from developing countries reporting resistance among serious community-acquired infections (including sepsis, pneumonia, and meningitis) in young infants.

Results: Only 10 relevant reports were retrieved. Among the 3 major pathogens studied (*Escherichia coli*, *Staphyloccoccus aureus*, and *Klebsiella* species), a high proportion of *E. coli* were ampicillin (72%) and cotrimoxazole (78%) resistant; 19% were resistant to third generation cephalosporins. Among *Klebsiella* species, almost all were resistant to ampicillin, 45% to cotrimoxazole, and 66% to third generation cephalosporins. Resistance to gentamicin was low among *E. coli* (13%), but much higher among *Klebsiella* species (60%). Methicillin resistance *S. aureus* (MRSA) was rare (1 of 33 isolates) but 46% were resistant to cotrimoxazole.

Conclusions: Antimicrobial resistance data for infections in young infants from community-based studies were extremely limited. Significant resistance, in particular to cotrimoxazole among all pathogens, and to gentamicin and third generation cephalosporins among *Klebsiella* and emerging resistance in *E. coli* is cause for concern. Limited data pose a challenge in devising simple community-based management strategies. Further studies from different developing country regions are needed to determine prevalence of resistant strains, as well as assess regional and time trends.

Key Words: neonatal infections, antimicrobial resistance, developing country, community

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Information regarding antimicrobial resistance among bacteria-causing infections in communities is essential for developing appropriate management strategies. In addition, the sustainability of community-based management strategies depends on monitoring changes in the etiology as well as resistance patterns of serious infections over time. Unfortunately, there is a paucity of information on resistance patterns of community-acquired infections in neonates and young infants in developing countries, owing to lack of appropriate laboratory and susceptibility testing facilities and challenges of conducting studies of etiology of serious infections in community settings.[1,2]

Hospital-based data show alarming rates of resistance to ampicillin and gentamicin among common pathogens causing neonatal sepsis (71% of *Klebsiella* and 50% of *Escherichia coli* are reportedly resistant to gentamicin), suggesting that the WHO recommended ampicillin and gentamicin combination for treatment of neonatal sepsis may no longer be effective in treating many newborns with sepsis.[3]

This review summarizes available data on antimicrobial resistance among common pathogens causing infections in neonates and young infants seen in community settings in developing countries–namely *Klebsiella* species, *E. coli*, and *S. aureus*.

METHODS

To identify studies documenting antimicrobial resistance in pathogens causing early onset or community-acquired neonatal sepsis, we searched PubMed database (date of last search May 7, 2007) from 1990 onward, using the words infant*, newborn*, neonat*, with resistance, resistant, susceptibility, sensitiv*, and infection*, bacter*, sepsis, septic*, meningitis, pneumonia, along with communit* or early. In addition, antimicrobial resistance or antibiotic resistance along with neonate was used. The search was combined with the names of all middle and low income countries, as defined by the World Bank.[4] Titles, abstracts, and/or full texts of studies obtained were screened. The search was supplemented with studies identified in other searches for this review series, as well as articles in the author's collection. Erroneous or inconsistent data were excluded. The analysis was restricted to the post 1990 period, owing to expected changes in resistance patterns over time making older data irrelevant. Resistance data for pathogens causing early onset sepsis (ie, within the first week of life) were included where available, as infections occurring during this period are commonly considered to be of maternal origin.[5]

RESULTS

Only 10 reports, including 2 unpublished works[6–13]; (Bhutta ZA 2005, unpublished data; Zaidi AKM 2008, unpublished data) contributed resistance data. Characteristics of these studies are presented in Table 1[6–13]; (Bhutta ZA 2005, unpublished data; Zaidi AKM 2008, unpublished data). Two studies provided resistance data for early onset sepsis or meningitis.[7,10] Five other reports used criteria to screen community-acquired infections[8,9,12]; (Bhutta ZA 2005, unpublished data; Zaidi AKM 2008, unpublished data), and only 2 of these reports were known to include data from predominantly home-born babies[12]; (Zaidi 2008, unpublished data).

The time trends in resistance rates are difficult to interpret, since data available for 1991 to 1995 were particularly limited (Table 2). Overall, methicillin resistant *S. aureus* (MRSA) did not appear to be a problem in these limited data (1 MRSA among 33 isolates in total). In data obtained from 1996 to 2007, nearly half of *S. aureus* isolates were resistant to cotrimoxazole. Nearly 90% of these isolates were obtained from a single African study done in the out-patient setting.[11] However, a similar proportion was also found to be resistant to cotrimoxazole among remaining isolates from other regions [12 from Pakistan (Zaidi 2008, unpublished data; Bhutta ZA 2005, unpublished data) and 1 from Philippines[12]].

Available data (Table 2) suggest that a high proportion of *E. coli* isolates were resistant to cotrimoxazole (78%) and ampicillin.

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TABLE 1. Studies With Resistance Data for Pathogens Causing Community-Acquired Infections in Young Infants

Author Year	Location	Setting/Hospital Type	Study Year	Age Group Considered	Notes
Adhikari et al 1995[6]	Durban, South Africa	General pediatric wards	1988–1991	Neonates	Meningitis in ward-admitted neonates
Kuruvilla et al 1998[7]	Vellore, India	Tertiary level care center	1995–1996	Within 48 h of birth	Early onset sepsis. All inborn babies
Lehman et al 1999[8]	Papua New Guinea	Outpatient department	1991–1993	Infants under 3 mo	Young infant sepsis study
Muhe et al 1999[9]	Addis Ababa, Ethiopia	Primary and tertiary care center	1991–1993	Infants under 3 mo	Young infant sepsis study
Laving et al 2003[10]	Nairobi, Kenya	Secondary level care center	1999	0–6 d	Early onset meningitis
Adejuygbe et al 2004[11]	Ile-Ife, Nigeria	Outpatient health center	2001	7–55 d	Study included infants not treated with antibiotics before presentation. Includes local infections
Quiambao et al 2007[12]	Bohol island, Phillipines	Community-acquired data from rural 1st level referral hospital	1994–2000	0–59 d	Data provided on request. Predominantly home-born
Milledge et al 2005[13]	Blantyre, Malawi	District and referral hospital	1996–2001	0–30 d	Most admitted from home (author provided information)
Bhutta ZA, 2005. Unpublished data	Karachi, Pakistan	Non-nosocomial data from tertiary hospital	1996–2005	0–27 d	Mostly hospital-born
Zaidi AKM, 2008. Unpublished data	Karachi, Pakistan	Community surveillance	2003–2007	0–59 d	Mostly home-born

TABLE 2. Resistance Patterns in Non-nosocomial Infections in Young Infants up to 90 Days of Age

Study Year	*Staphylococcus aureus*			*Klebsiella* species			*Escherichia coli*		
	No. Tested	No. Resistant	Resistant (%)	No. Tested	No. Resistant	Resistant (%)	No. Tested	No. Resistant	Resistant (%)
1991–1995									
Cotrimoxazole	12	0	0				5	2	40
Ampicillin/Amoxicillin	17	15	88	3	1	33	12	1	8
Gentamicin	17	1	6	3	1	33	12	1	8
Methicillin	5	0	0						
Chloramphenicol	12	0	0				5	1	20
Ceftriaxone, or other third generation cephalosporins	5	0	0	3	1	33	12	0	0
Amikacin				3	0	0	5	0	0
1996–2007*									
Cotrimoxazole	114	52	46	58	26	45	37	29	78
Ampicillin/Amoxicillin				123	119	97	105	76	72
Gentamicin	214	36	17	121	72	60	106	14	13
Methicillin	28	1	4						
Chloramphenicol	199	49	25	66	50	76	70	31	44
Ceftriaxone, or other third generation cephalosporins				65	43	66	42	8	19
Amikacin	12	1	8	61	26	43	34	5	15

*Includes 1 study from 1994–2000.

Among 12 *E. coli* isolates reported during the period of 1991 to 1995, only 1 was ampicillin-resistant (8%), but among 105 isolates from the 1996 to 2007 period, 76 (72%) exhibited resistance to ampicillin. Resistance to gentamicin was low (13%) among *E. coli*. However, 72 of 121 isolates (60%) *Klebsiella* were gentamicin resistant. Most *Klebsiella* (66%) were also resistant to third generation cephalosporins and emerging resistance among *E. coli* (19%) was also noted.

DISCUSSION AND CONCLUSIONS

The review underscores the paucity of data regarding resistance patterns among major pathogens causing infections in newborns and young infants in community settings in developing countries. Most studies on microbial etiology report pathogens but do not report resistance patterns. Such limited data preclude firm conclusions, and indicate the urgent need for further studies as well as establishment of infection surveillance and antimicrobial resistance monitoring and reporting systems in developing countries.

The data available suggest, however, that in contrast to hospital settings, resistance rates may not be as high in community-acquired infections. Resistance to gentamicin is much lower than that reported from hospital-based studies,[3] and the rare occurrence of MRSA among community-acquired infections is notable and in stark contrast to hospital-based studies from developing countries, where MRSA is now a major concern.[3] *E. coli* resistance to third generation cephalosporins was also less common compared with figures reported from hospital-based studies.[3]

Cotrimoxazole is an oral agent in widespread use in the management of acute respiratory infections in national pneumonia control programs in many developing countries. As the data here show, high-level resistance is now common among community

isolates of *E. coli* and *S. aureus.* Overall, 45% of *Klebsiella* isolates were resistant to cotrimoxazole; however, recent community-based data from Pakistan (Zaidi AKM 2008, unpublished data) show rates as high as 83%.

Of particular concern is the high level of resistance reported among *Klebsiella*, 60% of the isolates showing resistance to gentamicin. Since *Klebsiella* are uniformly resistant to ampicillin, regimens containing ampicillin and gentamicin would not provide adequate coverage against most *Klebsiella* species.

Increasing resistance to third generation cephalosporins among *Klebsiella* and *E. coli* is also notable. *Klebsiella* and *E. coli* resistance is usually acquired via plasmid-mediated extended spectrum beta-lactamase (ESBL) production.[14,15] Owing to the presence of other resistance-conferring genes on these transferable plasmids, such organisms are also often resistant to other drugs, including aminoglycoside antibiotics.[15] Risk factors for acquiring ESBL organisms include heavy antibiotic use, including use of third generation cephalosporins.[14,15] In a facility-based study of neonatal sepsis in India, 50% of babies with early onset gram negative sepsis were infected with ESBL producing bacteria[16]; however, the possibility of these being nosocomial, rather than maternally acquired infections cannot be ruled out. Further investigations are required to determine prevalence of ESBL and multidrug resistant *Klebsiella* and *E. coli* in young infants in community settings. Indeed, several studies of community-acquired urinary tract infections report that ESBL-mediated resistance among *E. coli* is now widespread.[17–22]

Although data are limited, antimicrobial resistance among community-acquired pathogens was higher than expected, especially the high level of ampicillin (72%) and ceftriaxone (19%) resistance reported in *E. coli*, and 60% gentamicin resistance among *Klebsiella*. However, the possibility that some isolates from early onset sepsis among hospital-born babies were in fact hospital rather than maternally-acquired, cannot be excluded. Additionally, many studies report microbiologic data without reporting clinical information on treatment and outcomes, which makes interpretation difficult.

The scarcity of data from community sources poses considerable challenges in devising optimal community-based antibiotic treatment guidelines for infections in young infants in developing countries. Moreover, ensuring rational antibiotic use, and preventing the spread of antimicrobial resistance is an important concern in implementing community-based antibiotic management strategies for serious infections in newborns and young infants. The critical gap in knowledge on newborn pathogens causing infections in home-born babies and their antimicrobial resistance patterns should be addressed soon if case-management guidelines for community management of serious infections in young infants are to be implemented at scale in developing countries where hospitalization of sick infants is often not feasible.

REFERENCES

1. Archibald LK, Reller LB. Clinical microbiology in developing countries. *Emerg Infect Dis*. 2001;7:302–305.
2. Herva E, Sombrero L, Lupisan S, et al. Establishing a laboratory for surveillance of invasive bacterial infections in a tertiary care government hospital in a rural province in the Philippines. *Am J Trop Med Hyg*. 1999;60:1035–1040.
3. Zaidi AK, Huskins WC, Thaver D, et al. Hospital-acquired neonatal infections in developing countries. *Lancet*. 2005;365:1175–1188.
4. The World Bank Country Groups by income. [The World Bank]. 2007. Available at: http://web.worldbank.org/WBSITE/EXTERNAL/DATASTATISTICS/0, contentMDK:20421402~pagePK:64133150~piPK:64133175~theSitePK:239419,00.html. Accessed May, 2007.
5. Klein JO. Bacterial sepsis and meningitis. In: Remington JS, Klein JO, eds. *Infectious Diseases of the Fetus, Newborn and Infants*. 5th ed. Philadelphia, PA: WB Saunders; 2001:943–984.
6. Adhikari M, Coovadia YM, Singh D. A 4-year study of neonatal meningitis: clinical and microbiological findings. *J Trop Pediatr*. 1995;41:81–85.
7. Kuruvilla KA, Pillai S, Jesudason M, et al. Bacterial profile of sepsis in a neonatal unit in south India. *Indian Pediatr*. 1998;35:851–858.
8. Lehmann D, Michael A, Omena M, et al. Bacterial and viral etiology of severe infection in children less than three months old in the highlands of Papua New Guinea. *Pediatr Infect Dis J*. 1999;18(suppl 10):S42–S49.
9. Muhe L, Tilahun M, Lulseged S, et al. Etiology of pneumonia, sepsis and meningitis in infants younger than three months of age in Ethiopia. *Pediatr Infect Dis J*. 1999;18(suppl 10):S56–S61.
10. Laving AM, Musoke RN, Wasunna AO, et al. Neonatal bacterial meningitis at the newborn unit of Kenyatta National Hospital. *East Afr Med J*. 2003;80:456–462.
11. Adejuyigbe EA, ko-Nai AK, Adisa B. Bacterial isolates in the sick young infant in Ile-Ife, *Nigeria. J Trop Pediatr*. 2004;50:323–327.
12. Quiambao BP, Simoes EA, Ladesma EA, et al. Serious community-acquired neonatal infections in rural Southeast Asia (Bohol Island, Philippines). *J Perinatol*. 2007;27:112–119.
13. Milledge J, Calis JC, Graham SM, et al. Aetiology of neonatal sepsis in Blantyre, Malawi: 1996–2001. *Ann Trop Paediatr*. 2005;25:101–110.
14. Paterson DL, Bonomo RA. Extended-spectrum beta-lactamases: a clinical update. *Clin Microbiol Rev*. 2005;18:657–686.
15. Paterson DL. Resistance in gram-negative bacteria: Enterobacteriaceae. *Am J Infect Control*. 2006;34(suppl 1):S20–S28.
16. Sehgal R, Gaind R, Chellani H, et al. Extended-spectrum beta lactamase-producing gram-negative bacteria: clinical profile and outcome in a neonatal intensive care unit. *Ann Trop Paediatr*. 2007;27:45–54.
17. Pitout JD, Nordmann P, Laupland KB, et al. Emergence of Enterobacteriaceae producing extended-spectrum beta-lactamases (ESBLs) in the community. *J Antimicrob Chemother*. 2005;56:52–59.
18. Arslan H, Azap OK, Ergonul O, et al. Risk factors for ciprofloxacin resistance among Escherichia coli strains isolated from community-acquired urinary tract infections in Turkey. *J Antimicrob Chemother*. 2005;56:914–918.
19. Akram M, Shahid M, Khan AU. Etiology and antibiotic resistance patterns of community-acquired urinary tract infections in JNMC Hospital Aligarh, India. *Ann Clin Microbiol Antimicrob*. 2007;6:4.
20. Marijan T, Vranes J, Bedenic B, et al. Emergence of uropathogenic extended-spectrum beta lactamases-producing Escherichia coli strains in the community. *Coll Antropol*. 2007;31:227–233.
21. Minarini LA, Gales AC, Palazzo IC, et al. Prevalence of community-occurring extended spectrum beta-lactamase-producing enterobacteriaceae in Brazil. *Curr Microbiol*. 2007;54:335–341.
22. Randrianirina F, Soares JL, Carod JF, et al. Antimicrobial resistance among uropathogens that cause community-acquired urinary tract infections in Antananarivo, Madagascar. *J Antimicrob Chemother*. 2007;59:309–312.