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# Challenges to the empiric management of neonatal sepsis using gentamicin plus ampicillin.

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**Abstract**

**Neonatal Sepsis (NS), sepsis occurring in children up to one month of life, is a leading cause of neonatal deaths in developing countries. The incidence of neonatal sepsis is higher in premature and low-birth weight infants, although most cases occur in full-term infants. Furthermore, the empiric treatment of patients with bloodstream infections (BSI) has become more complicated in an era of increasing antimicrobial resistance. Hence, the aim of this review article is to show the problem arising while using ampicillin plus gentamicin as mainstay therapy. A number of risk factors has been mentioned to increase the incidence of NS, in Early onset neonatal sepsis (EONS) maternal and neonatal factors (maternal infections, nutritional status of the mother, premature deliver, early rupture of membrane, prolonged delivery, underweight) has been implicated while in late onset neonatal sepsis (LONS) environmental factor (instrumental delivery, hospital admission…) taking the lead to cause NS. One study analyzed 19 different studies from 13 different developing countries on prevalence of microbes for causing sepsis in neonates and reported that, *Staphylococcus aureus, Klebsiella* spp. and *Escherichia coli* accounted for 55% (39-70%) of culture positive sepsis. Empirical treatment for neonatal sepsis, recommended in the current WHO guidelines is intravenous ampicillin (or penicillin) plus gentamicin for 7 days. The clinical questions are *how reliable to use ampicillin plus gentamicin in all settings? Are there any reports contrary to these guidelines? What should be the dosing interval of Gentamicin/ampicillin?* Some clinicians argue that, since majority of mothers in current practice are giving births at hospital setups, where *Staphylococcus aureus* is predominating, treatments of the standard guideline for NS has to be modified. Therefore, it will be important to evaluate all newly developed antibiotics in neonates to assure their maximum efficacy and safety.**

**Keywords**: Ampicillin, Gentamicin, Ampicillin plus gentamicin, Neonatal sepsis, Empiric management.

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## Introduction

Sepsis, defined by the international pediatric sepsis consensus conference, as a Systemic Inflammatory Response Syndrome (SIRS) in the presence of a suspected or proven infection [1]. Neonatal Sepsis (NS), sepsis occurring in children up to one month of life, is a leading cause of neonatal deaths in developing countries [2]. Some studies reported sepsis rate as 1.81 per 1000 pregnant women, while one study reported 2.91 per 1000 live births, but this figure can be as high as 24 (95% CI 21.8-25.7) for 1000 live births [3-6]. Generally, the incidence of neonatal sepsis is higher in premature and low-birth weight infants, although most cases occur in full-term infants [7]. Furthermore, the empiric treatment of patients with bloodstream infections (BSI) has become more complicated in an era of increasing antimicrobial resistance [8].

NS can be classified as Early-Onset Neonatal Sepsis (EONS) occurring within 72 h of periods, some authors prefers to extend this period up to one week; Late-Onset Neonatal Sepsis (LONS) occurring after 72 h, occurring after one week on the later classification; or Late-Late Onset Neonatal Sepsis (LLONS) occurring late in neonatal period but within one month of the infant life. However, if the sepsis is occurring after 28 days of the infant life the term neonatal sepsis may not be applicable [7,9,10].

A number of risk factors has been mentioned to increase the incidence of NS, in Early Onset Neonatal Sepsis (EONS) maternal and neonatal factors (maternal infections, nutritional status of the mother, premature deliver, early rupture of membrane, prolonged delivery, underweight, …) has been implicated the leading while in Late Onset Neonatal Sepsis (LONS) environmental factor

(instrumental delivery, hospital admission…) taking the lead to cause NS. One study from Mexico associated EONS with maternal age ≤ 15 years (OR 3.50; 95% CI 1.56-7.85), rupture of membranes >18 h (OR 2.65; 95% CI 1.18-5.92), maternal fever (OR 6.04; 95% CI 1.54-23.6), birth weight ≤ 2,500 g (OR 4.82; 95% CI 2.38-9.75) and gestational age<37 weeks (OR 3.14; 95% CI 1.58-6.22), while LONS and LLONS have been largely exemplified as an extension to the EONS and/or associated with environmental factors [10]. Attack rates of neonatal sepsis increase significantly in LBW infants in the presence of maternal chorioamnionitis, congenital immune defects, asplenia, galactosemia *(E. coli)* and malformations leading to high inocula of bacteria (obstructive uropathy) [7].

Studies reported that bacterial pathogens (predominantly Gram negative) with reduced susceptibility to empiric medication have been reported, with variations both between and within regions of the developing nations [11]. *Escherichia coli* (*E.coli*) were reported as predominant pathogens in EONS, followed by Group B Streptococcus (GBS), *Listeria monocytogenes* and Klebsiella species. While other studies putting GBS as a leading in EONS and *Staphylococcus aureus* in LONS [5,12]. *Staphylococcus aureus* and *Escherichia coli* mentioned as the leading for causing all types of NS [5,13]. Neonatal sepsis is often complicated with hypoglycemia possibly as a result of diminished caloric intake with impaired gluconeogenesis, cardiovascular disease, pneumonia, meningitis and acute kidney injury as a result of hematogenesis [7,14]. One study analyzed 19 different studies from 13 different developing countries on prevalence of microbes for causing sepsis in neonates and reported that, *Staphylococcus aureus, Klebsiella* spp. and *Escherichia coli* accounted for 55% (39-70%) of culture positive sepsis. In infants outside the neonatal period, the most prevalent pathogens were *S. aureus, E. coli, Klebsiella* spp., *Streptococcus pneumoniae* and *Salmonella* spp., which accounted for 59% (26-92%) of culture positive sepsis [15].

Group B streptococcal neonatal sepsis is a significantly underestimated problem. Epidemiologic studies revealed an incidence of 2 per 1,000 live births and a mortality rate of 1 per 1,000 live births. Vaginal cultures for group B were positive in 4.6 per cent of women at delivery, and 1.2 per cent of their infants had positive throat cultures [16]. A number of studies have demonstrated a significant reduction of neonatal sepsis by intrapartum chemoprophylaxis with ampicillin-penicillin in patients colonized with GBS. However, as the use of antibiotics continues to increase, in general, and in obstetrics, in particular, antibiotic resistance of some organisms becomes a significant concern [17].

Empirical treatment for neonatal sepsis, recommended in current WHO guidelines is intravenous ampicillin (or penicillin) plus gentamicin for 7 days. Empiric sepsis treatments are highly advocated in children considering many factors. One of the reasons is to avoid any dalliance in the management. Because, dalliance in initiating active therapy have been associated with worsened clinical outcomes. However, all patients with suspected sepsis should have appropriate cultures obtained side by side with empiric treatment [18]. All guidelines support to initiate sepsis treatment with ampicillin plus either Gentamicin or Cefotaxime [14]. The SCOUT study reported that Gentamicin (46%), ampicillin (39%) and oxacillin (8%) were used most frequently among 1607 infants studied in intensive care unit [19].

The use of gentamicin plus ampicillin has at least four fundamental advantages over the use of other antimicrobial in pediatric population, these include excellent evidence based clinical use in pediatrics for longer period, their synergistic effects, their broad spectrum activity and also the excellent activity of ampicillin to eradicate *Listeria monocytogenes*. However, beyond these, factors such as pharmaco-kineteic profiles, dosing intervals, safety and drug resistance reports should be analyzed carefully for the emerging challenges to the use of these medications [7]. The aim of this review article is then to show the problem arising while using ampicillin plus gnetamicin as mainstay therapy and the clinical question are how reliable to use ampicillin plus gentamicin in all settings? Are there any other contrary reports? What should be the dosing interval of Gentamicin/ampicillin? Furthermore, some clinicians argue that, since nowadays majority of mothers in current practice are giving births at hospital setups, where *Staphylococcus aureus* is predominating, treatments of the standard guideline for NS has to be revised as per evidence based medicine reports.

### *Treatment Outcomes of Ampicillin plus Gentamicin*

There has been an enormous increase in our knowledge of neonatal physiology and drug disposition. Fortunately, many of the antibacterial drugs used in neonates (e.g. penicillins and cephalosporins) are relatively safe. It will be important to evaluate all newly developed antibiotics in neonates to assure their maximum efficacy and safety [20]. Standardized reporting of treatment outcomes is required to evaluate practice, provide guidance on second-line regimes and for studies of new approaches, such as simplified community-based regimens, and to determine the appropriate duration of empiric treatment for apparently low-risk neonates with early resolution of clinical signs, or where available, negative blood cultures. Thus, a multifaceted approach, with attention to microbiological quality assurance, is needed to better guide antimicrobial use and reduce mortality and long-term impairments [11].

## Feasibility

Gentamicin for the treatment of neonatal sepsis is both feasible and effective in community-based settings and can be used as an alternative to the hospital based care in resource compromised settings [2,7]. Additionally, Aminoglcosides appear to be less nephrotoxic and ototoxic in neonates than in older patients, and the role of serum concentration monitoring should be limited to specific neonatal patients [20].

The problem in developing world, antibiotic susceptibility data are limited, available reports also suggest reducing

susceptibility to first-and second-line antibiotics in both hospital and community-acquired neonatal sepsis [18]. A number of studies showed that, there is no difference in either 'Once-Daily Dosing' (ODD) or 'multiple daily dosing' (MDD) with respect to 'Clearance of Sepsis'. A meta- analysis of RCT studies showed adequate 'Clearance of Sepsis' was equivalence in both ODD and MDD, [Typical RD 0.00 (95% CI-0.19, 0.19); 3 trials; N=36] [21].

## Dosing

Basically, studies showed that if gentamicin is given at a high dose once a day, it is just as effective as giving gentamicin 3 times a day, but there is less kidney damage, and giving gentamicin once a day is less expensive for hospitals [22]. One study compared eleven Randomized Or Quasi Randomized Controlled Trials (RCT/QRCT) studies for ODD to MDD of Gentamicin in newborn infants <28 days of life and it was found that all infants in both ODD as well as MDD regimen showed adequate clearance of sepsis [typical RD 0.00 (95% CI-0.19 to 0.19); 3 trials; N=36] [23]. The rationale for ODD promotion was based on two observations: the 1st is the damaging effects of gentamicin (and other aminglycosides) on the kidney cells is greater as the blood level of gentamicin or other aminoglycoside becomes higher as in cases of MDD, but only to a certain point when raising the serum aminoglycoside or gentamicin concentration has no further damaging effect, and ccertain bacteria continue to die for up to 8 h after the serum level of gentamicin drops below the 2 mg/L value (post-antibiotic effect, or PAE) [22].

Whereas, ampicillin is a beta-lactam antibiotic and is the most commonly prescribed drug in hospitalized infants. In spite of the frequency of use, the FDA label has no specific dosing of ampicillin for infants. Infants are recommended to take twice a day dose of ampicillin rather that a four time a day dose because of the physiological condition of children in which their liver is under functioning and they do possess relatively larger body water compared to the other age groups showing better volume of distribution of water (Vd) soluble drugs [7,24].

## Pharmacokinetic

PK studies in premature infants have been scarce, but studies are now more feasible with the emergence of ultra-low-volume assays, PK modeling and simulation, and opportunistic study designs [24]. Aminoglycoside CL is dependent on renal glomerular filtration which is markedly decreased in neonates, especially those preterm [20].

According to one study done in pediatric population, ODD showed superiority over MDD. The ODD Gentamicin regimen was associated with less failures to attain peak level of at least 5 µg/ml [typical RR 0.22 (95% CI 0.11 to 0.47); 9 trials; N=422] and less failures to achieve steady state trough levels of <2 µg/ml [typical RR 0.38 (95% CI 0.27 to 0.55); 11 trials N=503] compared to MDD regimen. Hence, ODD may be superior in preventing EONS conversion to LONS [21,23]. Similarly, in another study a higher number of patients in the ODD group showed favorable Gentamicin peak concentrations as compared with the MDD group (100% versus 87%). However, the MDD group in the later study showed a higher number of trough concentrations in the undesirable range as compared with the ODD group (17% versus 0%) [25]. The mode of dosing in both studies did not affect the volume of distribution; however, the t1/2 was significantly longer in the ODD groups. ODD was found to be cost-saving [26].

## Safety

In order to maximize therapeutic benefit and minimize drug toxicity, it is important to determine appropriate dosing regimens for pediatric population. Six different trials reported consistently measured ototoxicity outcomes in neonates treated with Gentamicin, and the pooled estimate for hearing loss was 3% (95% CI 0-7%). The report of nephrotoxicity was incomplete due to variation in case definitions used [27]. According to a meta-analysis report of six RCT/QRCT and another study on 123 children, there was no change in nephrotoxicity or auditory toxicity patter due to 'once a day' dosing or 'multiple doses a day' regimen [23,28].

A study done on a total of 79 children (median age: 5.6 years; range: 1 month-16 years) who were received 106 episodes of Gentamicin therapy 88% of them developed ototoxicity with Two patients (1.88%, 95% confidence interval: 0.10%-7.13%) experienced permanent hearing loss and 92% of them developed nephrotoxicity with One patient (0.94%, 95% confidence interval: <0.10%-5.73%) experienced transient nephrotoxicity. This figure was exaggerated due to the fact that 61% of them had neutropenia because of chemotherapy and cancer related complications. Two patients (1.88%, 95% confidence interval: 0.10%-7.13%) experienced permanent hearing loss [29].

### *Drug Susceptibility Patterns of Common Etiologies of Neonatal Sepsis*

Antimicrobial resistance (AMR) due to Klebsiella species was reported in 96-99% for WHO-recommended first line therapy (gentamicin and ampicillin/penicillin) to 94-97% for third generation cephalosporins [12]. One study also reported that 77% of the isolates were multidrug-resistant (60% of gram-positive bacteria and 83.4% of gram-negative bacteria) to all the available drugs for management NS in neonatal intensive care unit (NICU) such as ampicillin, amoxicillin, cefotaxime, ceftriaxone and Gentamicin [13].

Furthermore according to the report of one study, the overall resistance to the WHO recommended first line antibiotics for NS management was 100%, 92% and 42% for cloxacillin, ampicillin and gentamicin, respectively. For the second line drugs resistance was 45%, 40% and 7% for ceftriaxone, vancomycin and amikacin respectively; for the isolated bacteria such as *Klebsiella* spp. 14 (35%), *Escherichia coli* 12 (22.5%), Coagulase negative staphlococci 9 (30%), *Staphylococcus aureus* 4 (10%), and *Pseudomonas* spp. 1 (2.5%) [30]. Study conducted

in 5 European countries showed that around one third of Enterobacteriaceae were resistant to ampicillin+ or cefotaxime+gentamicin but only 10 % to meropenem [31].

Study also showed that for neonates, penicillin/gentamicin had comparable *in vitro* coverage to third-generation cephalosporin (57% vs. 56%). In older infants (1-12 months), in vitro susceptibility to penicillin/gentamicin, chloramphenicol/penicillin and third-generation cephalosporins was 63%, 47% and 64%, respectively (Table 1) [15].

Antibiotic resistance of GBS has been reported by many investigators and none of them reported that it is resistant to penicillin derivatives. Rather it was reported by some investigators the occurrence of some resistance to Macrolides–lincosamides–streptogramins. The WHO and CDC guidelines are focusing based on these facts, that NS can be treated by the combination of Ampicillin and gentamicin. However, the way empiric management focus should also target which etiologic agents are more prevalent in hospital setups of developing nations. A number of articles are reporting that the most prevalence etiologic agent causing NS (EONS or LONS) is *S. aureus*. For example, one article reported that the common isolates in blood culture from pediatric-neonatal population were *S. aureus* 41 (50.61%), coagulase negative staphylococci 10 (12.3%) and *K. pneumoniae* 10 (12.3%) [34]. Similar report has been seen by a number of investigators [35-37].

## Conclusion and Recommendation

The current WHO recommendation of antibiotics for empiric management of NS (Ampicillin plus gentamicin/ cefotaxime) is in line with a number of findings. However, improving local surveillance data using standardized antimicrobial susceptibility testing methods and validation of diagnostic algorithms against microbial findings are essential. Children taking Gentamicin should be closely monitored for overlapping toxicity from other insults causing **nephrotoxicity** and **ototoxicity**. However, there is no change in nephrotoxicity or auditory toxicity by using either ODD or MDD.

Some studies supports the use of extended-interval (single

***Table 1.*** *Antimicrobial susceptible to resistant ratio in percent, pooled database [17,32,33]*

| Antimicrobials | Antimicrobial class | *Pseudomonas aeruginosa* (n=/>161) | | *Escherichia coli* (n=/>134) | | *Klebsiella* spp. (n=/>117) | | *Enterobacter* spp. (n=/>92) | | Group B streptococcus (n=/>500) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | S (%) | R (%) | S (%) | R (%) | S (%) | R (%) | S (%) | R (%) | S (%) | R (%) |
| Penicillin | Ampicillin | 0 | 97.5 | 46.3 | 52.2 | 0.9 | 82.9 | 1.1 | 85.9 | 62.7 | 0 |
| | Amoxicillin/clavulanate | 0.6 | 97.5 | 74.6 | 13.4 | 86.3 | 6 | 1.1 | 96.7 | 100 | 0 |
| | Piperacillin | 83.2 | 16.8 | 56.7 | 33.6 | 70.9 | 24.8 | 70.7 | 19.6 | 100 | 0 |
| | Piperacillin/tazobactam | 87 | 13 | 95.5 | 3 | 89.7 | 6 | 73.9 | 8.7 | 100 | 0 |
| | Ticarcillin | 68.9 | 31.1 | 49.3 | 46.3 | 128 | 128 | 64.8 | 33 | 100 | 0 |
| | Oxacillin | 48.6 | 51.4 | 16.1 | 83.9 | ** | | * | * | 100 | 0 |
| | Penicillin or ampicillin | 68.3 | 31.7 | 69.4 | 8.2 | 77.8 | 12 | 65.2 | 29.3 | 98 | 0 |
| | Ticarcillin/clavulanate | 68.3 | 31.7 | 69.4 | 8.2 | 77.8 | 12 | 65.2 | 29.3 | 100 | 0 |
| Cephalosporin | Cefoxitin | 0 | 100 | 80.6 | 9.7 | 80.3 | 11.1 | 3.3 | 96.7 | 98.1 | 0 |
| | Cefuroxime | 0 | 98.8 | 84.3 | 7.5 | 74.4 | 17.1 | 50 | 37 | 100 | 0 |
| | Ceftazidime | 77 | 19.3 | 97 | 3 | 85.5 | 13.7 | 71.7 | 26.1 | 100 | 0 |
| | Ceftriaxone | 10.6 | 66.5 | 97 | 1.5 | 89.7 | 2.6 | 77.2 | 9.8 | 50 | 15.4 |
| | Cefepime | 80.1 | 8.1 | 100 | 0 | 98.3 | 1.7 | 98.9 | 0 | 100 | 0 |
| Other B-lactams | Aztreonam | 60.2 | 26.7 | 96.3 | 2.2 | 86.3 | 12.8 | 70.7 | 17.4 | 66.5 | 30.8 |
| | Imipenem | 78.3 | 16.1 | 100 | 0 | 100 | 0 | 97.8 | 2.2 | 100 | 0 |
| | Meropenem | 79.5 | 12.4 | 100 | 0 | 100 | 0 | 97.8 | 1.1 | 100 | 0 |
| Fluoroquinolones | Ciprofloxacin | 69.6 | 24.8 | 87.3 | 12.7 | 84.6 | 12.8 | 89.1 | 9.8 | 68.2 | 0 |
| | Gatifloxacin | 62.7 | 25.5 | 87.3 | 11.9 | 86.3 | 5.1 | 92.4 | 3.3 | 72 | 0 |
| Aminoglycosides | Amikacin | 96.9 | 3.1 | 99.3 | 0 | 95.7 | 3.4 | 97.8 | 1.1 | 82 | ** |
| | Gentamicin | 80.7 | 13.7 | 92.5 | 5.3 | 89.7 | 6.8 | 95.7 | 4.3 | 74 | ** |
| | Tobramycin | 87.6 | 12.4 | 96.3 | 3 | 86.3 | 7.7 | 94.6 | 5.4 | 76 | ** |
| Macrolides–lincosamides–streptogramins | Erythromycin | 36.7 | 63.3 | ** | ** | ** | ** | 13.7 | 56.9 | 65.4 | 25 |
| | Clindamycin | 56.1 | 43.9 | ** | ** | ** | ** | * | * | 80.8 | 19.2 |
| | Quinupristin/dalfopristin | 100 | 0* | 100 | 0* | 100 | 0* | 37.9 | 57.9 | 100 | 0 |
| Glycopeptides | Vancomycine | 100 | 0 | 100 | 0 | 100 | 0 | 70.5 | 28.4 | ** | ** |
| | Teicoplanin | 100 | 0 | 100 | 0 | 100 | 0 | 74.7 | 22.1 | ** | ** |
| Other classes | Chloramphenicol | 90.9 | 1.6 | 90.o | 1.6 | 91.9 | 1.9 | 86.3 | 8.4 | 100 | 0 |
| | Linezolid | 100 | 0* | 100 | 0* | 100 | 0* | 95.8 | 1.1 | ** | ** |
| | Tetracycline | 95.6 | 3.4 | 94.6 | 2.4 | 96.6 | 3.9 | 38.9 | 60 | 3.4 | 95.8 |
| Other B-lactams | Trimethoprim/ sulphamethoxazole | 96.2 | 3.8 | 95.2 | 4.8 | 97.2 | 3.5 | * | * | ** | ** |

* No interpretive criteria have been published; ** Limited data; S/R (%)=Susceptible to Resistant ratio in percent

daily, ODD) dosing in hospitalized children due to its efficacy and safety with the added advantage of needing fewer injections but some studies resist to recommend considering the limited number of available data to support ODD over MDD. A number of studies reported that pharmacokinetic properties of ODD Gentamicin regimen are superior to MDD regimen in that it achieves higher peak levels while avoiding toxic trough levels.

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