

## Use of oral Cotrimoxazole and injectable Gentamicin in module 6 & 7 of ASHA program

Dr. Shyam Ashtekar has raised some objections regarding the alleged use of oral Cotrimoxazole and injectable Gentamicin in module 6 & 7 of the ASHA program. Let us examine each objection and the evidence on it.

### **Objection 1: Use of Gentamicin in newborn**

Dr. Ashtekar raises false alarm that Gentamicin is included in the training of module 6 & 7. Module 6 and 7 do not recommend the use of injectable Gentamicin by ASHA. The modules recommend babies who need Gentamicin to be referred to health facility with a doctor (page 55 of Module 7).

- Dr. Ashtekar raises objection to the use of Gentamicin in newborns by doctors as well, on the ground that it can cause nephrotoxicity or oto-toxicity, and hence, should not be used at any cost. He refers to the opinion of the Committee of Experts appointed by Government of Maharashtra including Consultant Pediatrician from Mumbai. He also mentions that several textbooks recommend against the use of Gentamicin in newborns.
  - Newborn infection / sepsis is a fulminant illness with very high case fatality rate. The case fatality in the bacteriologically positive cases of newborn sepsis in the pre antibiotic era was 90% (The Yale series on newborn sepsis). Hence neonatology and pediatric textbooks recommend urgent initiation of antibiotic therapy without waiting for the reports of blood culture and sensitivity. In the absence of the facility of culture & sensitivity in the primary and secondary care setting, pediatric and neonatology textbooks recommend using injectable Gentamicin with one more antibiotic. There are at least 6 references for this guideline.
- 1) The 'Nelson's Textbook of Pediatrics', the bible world over, in the chapter on 'Infections of the Neonatal Infant' recommends the use of an injectable aminoglycoside antibiotic such as Gentamicin even in the facility setting. (Edition 18<sup>th</sup>, Chapter 109.8)
  - 2) The textbook 'Diseases of the Newborn' by Schaffer and Avery recommend that for newborn infection / sepsis 'Ampicillin in combination with Gentamicin is a reasonable choice' as initial therapy (Edition 9<sup>th</sup>, Part IX, Chapter 39, Page 547 – 550).
  - 3) Prof. Meharban Singh, former Head of the Department of Pediatrics and Neonatal Division, All India Institute of Medical Sciences recommends in the 'Manual of Essential Pediatrics' the use of injectable aminoglycoside such as Gentamicin as first choice for both community acquired as well as community acquired newborn sepsis.
  - 4) Prof Meharban Singh in the textbook, 'Care of the Newborn' recommends that in a rural setting rational choice of antibiotic should include gentamicin in combination with drugs such as ampicillin. He says that considering the spectrum of the microorganisms causing newborn sepsis in India (based on National Neonatal-Perinatal Network Database) in neonatal units in facilities, the logical initial choice of antibiotic would be a combination of an aminoglycoside (Gentamicin) with others.
  - 5) The textbook 'Essential Pediatrics' edited by Professor OP Ghai (formerly Dean AIIMS and Head, Department of Pediatrics) and Prof. Vinod Paul (current Head of the

Department of Pediatrics, AIIMS) recommend use of Gentamicin as the first line of drug for treatment of newborn sepsis.

- 6) The IMCI (WHO) program includes the use of injectable Gentamicin as the first line drug for treatment of serious newborn infection.

### **Objection 2: Use of Oral Cotrimoxazole in newborns**

Dr. Ashtekar raises objection to the use of oral Cotrimoxazole by ASHA for the treatment of newborn and childhood infections.

#### **1) What is the burden of newborn infections in India?**

- Every year there are approximately 10 lakh newborn deaths in India. Approximately a third of these deaths (3.3 Lakh) are due to newborn infections. If all of these 3.3 lakh newborns would receive Cotrimoxazole, that alone can reduce the case fatality rate due to newborn infection by 50%, potentially saving 1 Lakh 65 thousand newborn every year in India.
- Any evidence of side effects and alarmist scare against the use of Cotrimoxazole needs to be evaluated against the huge magnitude of this problem in India, and not on the basis of exaggerated scare of rare side effects, which is merely a theoretical possibility. It is difficult to find any case series or clinical or field trials which document this: Where and when did the side effects occur? How frequently?

#### **2) What are the advantages of use of oral Cotrimoxazole for newborn infections?**

- It has a wide spectrum of anti-microbial effect offering protection against both gram positive and gram negative microorganisms.
- It is thermostable and does not require cold storage.
- Ease of dosing (twice daily)
- It is cheap.
- Cotrimoxazole is already in use for childhood pneumonia as recommended by WHO / UNICEF in ARI program since 1992 and in the IMCI / IMNCI program in several developing countries and the community health workers are accustomed to use it.

#### **3) What is the evidence regarding safety of use of Cotrimoxazole for newborn infections and use of oral Cotrimoxazole aggravating jaundice in newborns?**

- There is not a single documented case of serious side effects of use of Cotrimoxazole in newborns. The apprehension about neurotoxicity caused by the use of Cotrimoxazole in neonates is only theoretical possibility. A review of world literature shows no such case happened anywhere.

*On the other hand, this apprehension is completely countered by following studies:*

- In a study published in J Pediatr (1982 Apr;100(4):647-50.) by Springer C et al, administering IV Cotrimoxazole to newborns of less than 3 days age, neither adverse side effects were seen during treatment nor did the displacement of bilirubin occur (as suspected) at therapeutic concentrations of Cotrimoxazole, nor was jaundice aggravated.
- In a recently (2003-2010) conducted trial of HBNC by ICMR in 5 states, oral Cotrimoxazole was used for treatment of newborn infections by community health

workers in area of 10 PHCs and by Anganwadi Workers in 10 PHCs. A DSMB intensively monitored incidence of any side effects with established protocols of immediate reporting of side effects. No serious side effects due to the use of antibiotics were recorded.

- In ANKUR trial in Maharashtra conducted at 7 different sites in 91 villages and 6 slums from 2003 to 2005, oral Cotrimoxazole was used for treatment of newborn infections by community health workers. Not a single case of side effects was recorded.
- In 39 villages of Gadchiroli, oral Cotrimoxazole is being used since 1988 for treatment of newborn pneumonia. In the 628 cases treated so far, not a single case of side effects has been recorded.

In the past 20 years nearly 1400 newborns with suspected pneumonia or sepsis have been treated with Cotrimoxazole alone (1988 – 95) or with Cotrimoxazole + Gentamicin (1996 – 2011) in the Gadchiroli field area of SEARCH.

In a follow-up survey in 2010 – 11 of the field area, all children of age 6 – 14 years in the area were visited, interviewed and those with suspicion were examined by a medical team visiting each village. We found that:

- a) There was not a single case of child with neurological abnormality suggestive of kernicterus (which is caused by aggravation of Jaundice) during newborn period – the main suspected.
- b) The prevalence of deafness was very low, and was similar in the intervention area and the comparison Government area.

Thus there was not a trace of evidence that treatment with Cotrimoxazole (1381 newborns) and with additional gentamicin (753 newborns) caused any harm. On the contrary this treatment averted an estimated 230 newborn deaths.

*The verdict of the field evidence is clear.*

### **3) What is the evidence regarding safe and effective use of Cotrimoxazole for newborn infections?**

There is strong evidence for use of oral Cotrimoxazole for newborn pneumonia / infections from multiple field trials conducted in developing countries.

- a) A systematic review by Zaidi et al (in BMC Public Health 2011) of 4 field trials using oral Cotrimoxazole for newborn pneumonia and sepsis shows 42% reduction in pneumonia specific mortality rate and 25% reduction in all cause NMR. Zaidi concludes that ‘...oral or injectable antibiotics alone (administered in the community) are highly effective in reducing deaths from newborn sepsis and pneumonia’.
- b) A metaanalysis of 4 field studies by Theodoratou et.al (International Journal of Epidemiology 2010;39:i155-i171) also shows 42% reduction in ALRI mortality by community based case management approach using Cotrimoxazole.
- c) The metaanalysis by Sazwal and Black published in Lancet Infectious Disease 2003 identified treatment of newborn pneumonia by oral Cotrimoxazole as an effective, evidence based intervention for the use in the community. According to them, the

treatment of newborn pneumonia / infection by antibiotic has potential to reduce All Cause Mortality by 27% and Pneumonia specific mortality by 20%.

*None of the metaanalysis report any untoward effects of the use of Cotrimoxazole in newborns.*

- d) The Lancet Neonatal Health Series 2005 has identified use of antibiotic in newborn pneumonia / infection as one of the selected community based intervention for global scaling up with the potential to reduce all cause newborn mortality by 27% .
- e) The Lancet Child Survival Series 2003 has also identified use of antibiotic in newborn pneumonia / infection as one of the selected effective community based intervention.
- f) In Gadchiroli, community health workers are using oral Cotrimoxazole for treatment of newborn infection since 1988. A series of research publications (Lancet 1989, Arch of Dis Child 1993, Lancet 1999 and J. Perinatology 203) have presented the scientific evidence from this field. In cases of newborn sepsis where only oral Cotrimoxazole was used, the case fatality rate reduced from 26% to 12.9%, and where both Cotrimoxazole and Gentamicin were used, the case fatality rate reduced to 6%.

*Thus universal access to only Cotrimoxazole can potentially prevent half of the deaths due to newborn infections, and to both the antibiotics can avert nearly three fourth of the deaths due to infections.*

- g) When pregnant women have HIV, there is a risk of infection transmitting to the newborn. Even in case of suspicion of newborn contacting HIV, WHO guidelines recommending daily Cotrimoxazole prophylaxis for HIV-infected pregnant women' (Forna F et.al: AIDS Rev. 2006 Jan-Mar;8(1):24-36), even if the drug is passed to the newborn through breast milk.

#### **4) What are the expert group recommendations regarding the use of oral Cotrimoxazole for treatment of newborn infections by ASHA?**

- a) The Presidents of the Indian Academy of Pediatrics and the National Neonatology Forum of India in two separate national workshops held in Gadchiroli (1999 and 2003) unanimously endorsed the use of oral Cotrimoxazole for newborn infections (and injectable gentamicin) as in the Home-based Newborn Care package to be scaled up nationally.
- b) The 'Technical Advisory Group' of Government of India for ASHA program in 5 states with representatives from the Ministry of Health and Family Welfare of Government of India, ICMR, WHO, UNICEF, Indian Academy of Pediatrics, National Neonatology Forum, IMNCI (WHO), Jan Swasthya Abhiyan and others endorsed the use of oral Cotrimoxazole for newborn infections by ASHA in the national program 2005 – 06). The module 6 & 7 are based on the recommendations of this national expert group (annexure 1).
- c) The IMNCI program includes the use of oral Cotrimoxazole as the first line drug for treatment of newborn superficial infections with certain precautions. (Ref. IMNCI guidelines, Government of India Ministry of Health, WHO and UNICEF, 2005).

- d) The WHO guidelines include the use of oral Cotrimoxazole as the first line drug for treatment of newborn pneumonia with certain precautions (Ref. The management of acute respiratory infection in children: Practical guideline for outpatient care, WHO 1995).

**Statement 1:**

Dr. Ashtekar recommends the use of oral Amoxicillin for treatment of newborn infections.

**A) What is the evidence for use of Amoxicillin to treat newborn infections?**

Dr. Ashtekar strongly proposes the use of Amoxicillin and is endorsed by the Committee of Experts appointed by the Government of Maharashtra. There is no particular reason to favor one antibiotic over other. Currently there is strong evidence regarding the safety and effectiveness of use of Cotrimoxazole. There has been only one field trial so far from Zambia (BMJ 2011;342:d346 ) in which Amoxicillin was used by TBAs for newborn infections. Though the trial reported reduction in the newborn mortality due to asphyxia, it did not find reduction in newborn mortality due to infections.

Hence let field trials be conducted in multiple setting using Amoxicillin and evidence emerge through trials, metaanalysis and systematic review for Amoxicillin. In the absence of such evidence, recommending Amoxicillin will be a subjective decision, not evidence based.

Oral Amoxicilling used with clavulanate

**Statement 2:**

Dr. Ashtekar refers to the Committee of Experts appointed by Government of Maharashtra and the guidelines recommended by this committee regarding the use of antibiotics by ASHA for newborn infections.

**Comment on the guidelines recommended by this Committee:**

- It is possible that the experts were not aware of the global evidence from field studies in developing countries as well as the accepted global guidelines or decided not to consider the evidence.
- Developed countries as well as the clinicians from private tertiary care setting from have at their disposal many options of antibiotics when they work in NICU. Nevertheless, one must learn to distinguish between the guidelines developed for clinical use in the developed countries or in the tertiary care setting and the guidelines for public health use, in community setting. Not doing so will be missing the public health approach to reducing newborn deaths.

**Conclusion:**

- 1) Newborns with suspected infections immediately need antibiotics. Nearly 3, 33,000 newborns are dying every year in India alone due to infections. The choice of antibiotic must be guided by evidence only. Current global evidence and guidelines recommend the use of Oral Cotrimoxazole by community health worker such as ASHA as effective and safe choice for management of newborn infections, if referral can't be enforced.

- 2) Current global evidence and guidelines recommend use of Gentamycin by PHC medical officers in clinical setting as a safe and cost effective practice for treatment of newborn infections. It is absurd to suggest a regressive practice of withholding Gentamicin from medical officers. Instead of asking the question – which approach will save more lives, such suggestions give exaggerated importance to the possibility of rare side effects and kill newborns with infections.
- 3) Recommendation of the use of oral Amoxicillin is limited by the lack evidence from field trial.
- 4) Every medicine has some side effect. A medicine without any side effect might not have any benefit as well. In short, no antibiotic is ideal. Hence we all make weighted choices. Therefore in the face of a life threatening situation, an oral antibiotic (extensive evidence is available for Cotrimoxazole) by CHW (ASHA) and oral + injectable by a PHC / CHC Medical Officer should be acceptable as viable alternative till a referral is possible.

To conclude, Dr. Ashtekar rightly points out that “...we all make mistakes till we are exposed to better info/advice is available.” And “...what is the problem regarding correcting our mistakes that may affect lives of so many?” In view of this evidence, not only the guidelines regarding use of Cotrimoxazole by ASHA should stand, but the PHC medical officers should be continued to be allowed to use injectable Gentamicin.

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