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Brief Communication

Managing Severe Malaria in the Era of Pre-elimination

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Abstract:

Severe malaria is a medical emergency mainly caused by falciparum parasite responsible for nearly 584,000 annual deaths globally in 2013.Most deaths in malaria happens in endemic countries before the patient reaches hospitals or within short period after admission; support of Intensive Care Unit (ICU) for optimum treatment of severe malaria is not available in many endemic countries. WHO recommends confirmation of diagnosis by immunochromatographic rapid test or by blood film examination and for treatment to use artemisinin based combination treatment (ACT) for uncomplicated falciparum malaria and thus reduces the incidence of severe malaria. Treatment recommended for severe malaria is IV artesunate for at least 24 hours followed by full dose oral ACT on recovery of per os status. Early feeding in unconscious patient of severe malaria increases the possibility of aspiration pneumonia. A single dose of rectal artesunate reduces death by 25% when used at a community level as pre-referral treatment and completion of treatment follows after admission. Single dose of primaquine 0.25 mg/kg is recommended for reduction of transmission. District hospitals in high endemic area should have facility of dialysis and referral Medical College Hospital should have functional ICU for further reduction of malaria death.

'A 10-year-old girl was admitted in a primary health care hospital (also called Upazilla Health Complex, UZHC) in Cox's Bazar, Bangladesh at 21 hours with history of fever for 05 days. Pre-hospital support for fever was only over the counter un-named drug from local medicine shop. For two days she was having vomiting and high coloured urine;on the day of admission in UHC, she had impaired consciousness for few hours and she had a generalized tonic clonic seizure one hour before admission. Physical examination revealed Glasgow Coma Score (GCS) 8, severe anaemia (Hb <6gm/dl), mild jaundice, hepatomegaly, hurried respiration, bilateral retinal haemorrhage in fundoscopy.Blood film was positive for Plasmodium falciparum, and S. creatinine was 3.8 mg/dl. She received IV artesunate on admission, one unit of fresh whole blood transfusion from prior identified donor at mid night. Arrangement of transfer to Chittagong Medical College Hospital (CMCH), Chittagong was made with public ambulance at 04 hour next day with a telephonic arrangement to transfer the patient to dialysis unit from the emergency room of CMCH, had an early evaluation made within half an hour of admission at 08 hour and had a haemodialysis at 8:30 hour. When she developed ARDS in next few hours she required assisted ventilation made available in the same hospital. Unfortunately the patient died on the same day following multi-organ failure (MOF).'

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Note: Ramu was the study site for 'paracetamol study for prevention of AKI' at the time of admission of the patient.

Severe malaria is an emergency situation mainly caused by P. falciparum and is responsible for nearly 584,000 annual deaths (uncertainty range 367 000–755 000) globally in 2013.[1]Most of the deaths in malaria happens in resource limited endemic countries even sometime before reaching small hospitals; support of Intensive Care Unit (ICU) for such a critically ill patient is a norm in the developed countries which is not available in the countries having burden of malaria, Bangladesh is not an exception. WHO recommends early parasitological diagnosis by immunographicrapid diagnostic test (RDT) or blood film examination, and for treatment to use artemisinin based combination treatment (ACT) for the treatment of uncomplicated falciparum malaria and thus reducing the incidence of severe malaria. In Bangladesh the recommended ACT is six dose of artemether-lumefantrine. Community based deployment of diagnostics and drugs were made to access for the patients even in remote areas by a government and non-government partnership in Bangladesh since such a regimen adopted in 2004 widely used since 2009.[2] The scenario was changed drastically in the last five years to reduce the cases of malaria below 30,000 and death to 15 in 2013[3] and this prompted the national malaria control program to plan for phase wise elimination of malaria by 2020 with the goal of 'zero death'.[4] Meanwhile some districts are considered to be in pre-elimination. A single dose of primaquine (0.25 mg/kg) has been recommended as transmission reduction strategy in such a situation and testing for glucose-6-phosphate dehydrogenase (G6PD) deficiency is not required.[7]Although an upsurge of malaria happened in the hill districts of Bangladesh in 2014 which is under evaluation.

Severe malaria includes a constellation of clinical and laboratory features in patients having positive blood film for plasmodium falciparum, varies from severe prostration to coma (GCS<11 in adults or a Blantyre coma score <3 in children), lung, renal involvement, severe anaemia, jaundice,

acidosis, classical retinal findings; at times add on phenomenon of complications occur with multi organ involvement causing increased probability of death.[5]Rarely P. vivax and knowlesi malaria can cause severe malaria which is yet to be reported from Bangladesh. In small hospitals relatively less severe form of severe malaria are admitted and patients with multiple organ involvement are referred to higher facilities. Unfortunately death with such patients are many folds higher.[6]WHO Malaria treatment guideline has been reviewed in 2015,[7] Bangladesh new regimen is in the phase of preparation. Key recommendations for drug treatment of severe malaria are use of IV artesuante at a dose of 2.4 mg/kg body weight per dose at 0, 12 and 24 hr and daily until attainment of reliable per of status followed by full dose of oral ACT. Artesuante is recommended irrespective of pregnancy status (including infants, pregnant women in all trimesters and lactating women) considering the much superiority over quinine in saving lives irrespective of age.[8,9,10] In children below 20 kg body weight a higher dose is recommended 3mg artesunate/kg per dose to ensure equivalent exposure to the drug. A single dose of rectal artesunate has been found to reduce death by 25% when used at a community level as pre-referral treatment and completion of treatment follows after admission and evaluation in resource limited situation has been incorporated as WHO recommendation as well.[7,11] Early enteral feeding is detrimental in patients with cerebral malaria treated in resource poor setting where endotracheal intubation is not generally available, rather early enteral feeding increases the risk of aspiration pneumonia (33%) and convey no clear benefits.[12]Malarial retinopathy is highly specific for cerebral malaria and these spectrum consist of four components retinal haemorrhage, retinal whitening, vessel discoloration and papilloedema. Ophthalmoscopic examination has diagnostic and prognostic utility at the bedside including when assessed by a non-specialist using direct ophthalmoscopy[13,14]. It is a very quick bed side clinical test that can guide a diagnosis in a suspected case of severe malaria as malaria parasite may be present as a by stander in a carrier in endemic area.

The vignette presented above deserve some discussion:

Despite promotion, early diagnosis and prompt treatment seeking is yet not found to be widely practiced by the community. A recommended 24-48 hour time frame is yet to be seen in getting diagnosis and treatment of uncomplicated malaria. In a recent visit to a sub-district hospital in Banderban, a number of patients even from a same family did not receive early diagnosis and treatment in the community as we committed.

Case Study:

Five cases of malaria admitted in an UZHC, Banderban, Bangladesh on April 7, 2015

1. 30-yr-old male, plantation worker (Jhamchari) had fever for 6 days- went to a local village shop received antimalarial treatment by self purchase- admitted to UZHC as an UM- treatment received: Ciprofloxacin + inj. Artesuante
2. (i) 25-yr-old male, rubber plantation worker, Dhochari, Chagalkhyia, Naikhongchari, Banderban 3 members of the same family (Figure 1) were admitted to UZHC. Fever for 2 days Inj. Artesunate; (ii) & (iii) 3.5-year-old child, and 25-year-old female pregnant 1st trimester treatment- Inj. Artesunate. Tablet quinine was not available in the hospital, date expired quinine was available.
3. 37-year-old wood cutter Jhailachari, no health worker around, had fever for 2 days- treatment received- inj. artesunate.

Figure 1: Three cases of malaria from same family admitted in an UZHC, in Chittagong Hill District. The patients and patient's parents provided verbal permission for publication of images.

Observation: Five **c**ases of uncomplicated malaria admitted and were receiving injection artesunate and tab ciprofloxacin. Case 1 of pregnancy in 1st trimester receiving inj. artesuante

Cases 4 received treatment beyond 48 hrs of illness. Cases 4 received primaquine 0.75 mg/kg body weight. Oral quinine was not available at this hospital

A prompt resuscitation has been found to be possible as done in this vignette even in small upazilla hospital is encouraging so also to have a functional referral for useful intervention by haemodialysis within an hour of admission is a praiseworthy action for a public facility which may not be a norm. The mid-term review 2014 found lack of logistics and resources for management of complications for example facilities of dialysis (at least peritoneal dialysis) close to their home and suggested to have such facilities in district hospitals in malaria endemic area Chittagong Hill District for example.[3]Daily intermittent haemodialysis (HD) versus peritoneal dialysis (PD) in patients of AKI showed no difference in survival or recovery of renal function.[15] Studies in India found a mortality in patients with PD was lower than with HD (20% vs 36%)[16].

During an attempt of verbal autopsy of >40 cases of fatal severe malaria deaths by (National Malaria Control Programme (NMCP) in 2014 a number of similar cases of severe malaria did not receive early diagnosis at the

community which requires further exploration. Although a pre-referral treatment is recommended for prevention of deaths from severe malaria we are unable to provide the feasible treatment persistently which is disheartening[11].

In order to have 'zero death' as a part of elimination of malaria 2020[4]all efforts should be made to diagnose and treat all the cases of uncomplicated falciparum malaria promptly using effective ACT based drug, uncomplicated vivax malaria with three-day-chloroquine and 14 day primaquine, quickly refer the patients of severe malaria with a pre-referral treatment (rectal artesunate in children), have a quick access to evaluation at sub-district hospital, and IV artesunate and other recommended supportive treatment close to home. District hospitals in Chittagong Hill Tract districts should have facility of dialysis at least PD and referral Medical College Hospital should have functional facility of ICU care.

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