Failure of Secondary Prophylaxis with Erythromycin in Rheumatic Heart Disease

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Background: Erythromycin is recommended for secondary prophylaxis in children with rheumatic heart disease, who are allergic to penicillin. **Case Characteristics:** A 9-year-old girl, with rheumatic heart disease, on secondary prophylaxis with erythromycin 250 mg BD, presented with acute rheumatic fever. **Outcome:** Responded to steroids and started on a higher dose (250 mg TDS) of erythromycin for secondary prophylaxis. **Message:** There is need to document the resistance of group A streptococci to erythromycin.

Key words: *Erythromycin, Rheumatic heart disease, Prophylaxis, Resistance.*

CASE REPORT

A 9-yr-old girl, known case of rheumatic heart disease presented with complaints of progressive breathlessness for 2 years with recent worsening (NYHA grade II to III), fever and migratory joint pain (bilateral knee) for 10 days. There was history of orthopnea, palpitations and chest pain. There was no history of sore throat, skin rash, abnormal body movements, emotional lability and hemoptysis. She was diagnosed in 2011 with acute rheumatic fever with severe mitral regurgitation, moderate aortic regurgitation and mild tricuspid regurgitation. Supportive treatment was started and she was put on secondary erythromycin (250 mg BD) prophylaxis as she was allergic to benzathine penicillin. During follow-up, good compliance to erythromycin was noted.

On examination, child was febrile with a pulse of 110/min, respiratory rate 48/min, BP- 130/50 and raised JVP. There was no pedal edema, clubbing, lymphadenopathy, cyanosis, rash, subcutaneous nodules and features suggestive of infective endocarditis. Cardiovascular examination revealed downward and outward hyperdynamic apex beat and a grade IV pansystolic murmur in the mitral area radiating to the axilla and grade III early diastolic descrescendo murmur in the aortic area. Respiratory system revealed bilateral basal crepitations while hepatomegaly was noted on abdominal examination.On musculoskeletal examination there was no evidence of arthritis. Central nervous system was normal.

Investigations revealed hemoglobin of 12.1 g%, total leucocyte count- 10,800 mm^3 (with 70% polymorphs), ESR of 50 mm/h, positive ASO (>400U/dL), CRP (6.89 mg/dL), anti DNAse B (471U/mL). ECG showed prolongation of PR interval (0.18sec) and left axis deviation. Throat swab and blood culture showed no growth. Cardiomegaly was evident on Chest *X*-ray while ECHO revealed dilated LV, pathological severe mitral regurgitation, moderate aortic regurgitation and mild tricuspid regurgitation. Anterior mitral laflet tip was thick (5 mm) with elbow deformity and restricted leaflet motion. There was no pericardial effusion and EF was 65%.

A diagnosis of recurrent acute rheumatic fever with congestive heart failure was made. Oral prednisolone was started and tapered after 4 weeks while aspirin was added. She responded and her ESR levels gradually decreased. Since recurrence occurred despite good compliance and adequate dose of erythromycin, serum erythromycin levels was planned but was not available. MIC levels could not be ascertained as the throat culture was negative. Patient was started on secondary prophylaxis of erythromycin albeit at a higher dose (40mg/kg *i.e.* 250 mg tds).

DISCUSSION

Children with RHD have a high risk of recurrence of acute rheumatic fever subsequent to Group A Streptococcus (GAS) pharyngitis. Primary prevention is achieved by intramuscular repository preparation of penicillin and its derivatives and/or oral penicillin until penicillin allergy is documented wherein oral macrolides, cephalosporins and clindamycin are recommended [4]. GAS resistant to penicillin have not been reported though there are reports of rising MIC levels [5]. While administering primary prophylaxis repeated course of antibiotics are not needed in asymptomatic patients who continue to harbor GAS after appropriate therapy, however a second course of antibiotics should be started in patients with previous history of rheumatic fever in themselves or in their family members. Failure to eradicate GAS from the throat usually occurs while using oral penicillin than intramuscular preparation and in

children who are chronic carriers with prolonged oral colonization of the bacteria [6].

Both asymptomatic and optimally treated acute symptomatic pharyngeal GAS infection can trigger recurrence. Therefore continuous antimicrobial prophylaxis (secondary prevention), the duration of which is guided by several risk factors including the age, socioeconomic strata of the patient and most importantly the severity of cardiac injury at the time of initial ARF provides the most effective protection from recurrence. Intramuscular Benzathine Penicillin every 3-to-4 weekly is recommended [4]. Diminished susceptibility of *Streptococcus pyogenes* to penicillin has been reported globally, but the literature on this is sparse from India [7,8]. Those who are allergic to penicillin are started on alternate antibiotics like oral macrolides (erythromycin/ azithromycin) or sulfadiazine. There have been reports worldwide of rising MIC level to macrolides too over the past decade [8].

The three major resistance genes found in Group A B hemolytic streptococcus are *erm* (A), *erm* (B), and *mef* (A). Macrolide resistance has been conferred to *mef* (A) gene [9]. Brahmadathan, *et al*. [10] studied the susceptibility of Group A B hemolytic streptococcus to penicillin and erythromycin over a period from 1986-2002 and concluded that there was a significant rise in erythromycin resistance. Erythromycin resistance was 2% in 1987, 2.7% in 1994, 5.8% in 1999 and 13.8% in 2002 [10]. Similar results were reported (17.6%) and by Ray, *et al*. (4%) [5,7]. Latania, *et al*. [8] reported a case of ARF which was treated with 10 days of azithromycin with no response. Throat culture revealed macrolide resistant GAS.

In our case the diagnosis of recurrence was based on modified Jones criteria but in absence of a positive throat culture and susceptibility reports the resistance pattern could not be adequately addressed. However the report highlights the importance of continuous monitoring of susceptibility pattern in order to observe the development of resistance over a period of time. Pediatricians must be aware of GAS resistance while treating patients with initial episode or recurrence of ARF so as to prevent the development of severe RHD which is usually a result of recurrent ARF.

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