Original Article

Etiological Aspects of Penicillin-Failure in the Treatment of Tonsillitis and Pharyngitis Caused by Group A, Beta-Hemolytic Streptococci (GABHS)

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ABSTRACT

Objective: To observe and study the cause of penicillin-failure and to see the therapeutic effects of other drugs and find out more effective and better remedy.

Study Design: A Retrospective study

Place and Duration of Study: This study was conducted in Microbiology Department, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre, National institute of Child Health from April 2004 – June 2005.

Materials and Methods: A total of 300 children attending OPD's and admitted (250 suspected and 50 Normal as control cases) of age group 5 – 15 years were included in this study.

Result: Drug sensitivity pattern of *streptococcus pyogenes* isolated in infected and control children was observed. Antibiotic discs used were Penicillin (10) units and Erythromycin(15 micrograms). The organism isolated GABHS shows 100% sensitivity to penicillin, while in case of erythromycin, it was sensitive in 24(85.7%) infected cases and resistant to 4(14.3%) cases.

Conclusion: Pharyngotonsillitis is a disease of poor community, the therapy with penicillin is economical compared with Cephalosporin group. Penicillin therapy is helpful in preventing the supporative and n supporative complications caused by GABHs.

Key Words: Penicillin Group A, beta hemolytic streptococci Beta-lactamase.

INTRODUCTION

Apart from its excellent in vitro efficacy, the repeated reports of the inability of penicillin to eradicate group-A, beta hemolytic streptococci (GABHS) from patients with acute and relapsing tonsillitis was concerned cause. Over the past 50 years, the rate of penicillin failure had constantly increased from about 7% in 1950 to almost 40% in 2000.[1]

Several explanations exist for the failure of penicillin to eradicate GABHS tonsillitis. One explanation was the poor penetration of penicillin into the tonsillar tissues as well as into the epithelial cells[2].

Other explanation relates to the bacterial interactions between GABHS and the other members of the pharyngo-tonsillar-bacterial flora. It was hypothesized that the enzyme beta-lactamase which was secreted by beta-lactamase producing aerobic and anaerobic bacteria, that colonize the pharynx and tonsils, may "shield" GABHS from pencillins[3].

These organisms include S.aureus, H.influenzae, and provetella, porphyromonas and Fusobacterium spp[4].

A recent increase was noted in the recovery of MRSA which was isolated from 16% of tonsils, making it more difficult to eradicate this and other beta-lactamase producing organisms. [5]

Another possibility was the co-aggregation between Moraxella catarrhalis and GABHS, which could facilitate colonization by GABHS.[6]

Increased recovery of Moraxella catarrhalis and Haemophilus influenza in association with group A beta haemolytic streptococci in healthy children and those with pharyngo-tonsillitis.[7]

Normal bacterial flora could interfere with the growth of GABHS.[8,9]

The absence of such competitive bacteria made it easier for GABHS to colonize and invade the pharyngo-tonsillar area.[10]

GABHS could also be reacquired from a contact or an object (i.e, toothbrush or dental braces)[11]

Bacteriologic and clinical treatment failures occur with penicillin, as with all antibiotics. Bacteriologic failure was failure to eradicate the streptococcal organism responsible for the original infection. Patients with this type of treatment failure might present with symptoms or be symptomatic. Some infected but asymptomatic patients might be carriers. Patients who remained symptomatic despite treatment were considered clinical failures and must be retreated. Study conducted over the past 40 years had reported penicillin bacteriologic failure rates ranging from 10 to 30 percent and clinical failure rates ranging from 5 to 10 percent.[12]

Penicillin had been the agents of choice for the therapy of a variety of bacterial infections. However, within the past sixty years, an increased resistance to these drugs had been noted. In addition to bacteria long known to resistant penicillin, such as Staphylococcus aureus and Enterobacteriaceae, other previously susceptible organisms became increasingly resistant due to several mechanisms including the production of the enzyme beta-lactamase(BL), these include aerobic and facultative bacteria such as Haemophilus influenza, Moraxella catarrhalis, as well as anaerobic gram-

negative bacilli(AGNB, i.e, Bacteroides fragilis group, pigmented Prevotella and Porphyromonas, Prevotella bivia, and Prevotelladisiens) and Fusobacterium SPP.[13]

Beta-lactamase- producing bacteria (BLPB) had a important clinical role in infections. These organisms can be pathogenic in causing the infection as well as had a indirect effect through their ability to produce the enzyme BL into their environment. BLPB might not only survive penicillin therapy but also might protect other penicillin-susceptible bacteria from penicillin by releasing the free enzyme into their environment.[14]

Animal studies demonstrated the ability of the enzyme BL to influence poly- microbial infections. BL producing of AGNB protected a penicillin-sensitive Fusobacterium necrophorum and group A beta hemolytic streptococci(GABHS) from penicillin therapy in mice. Clindamycin or the combination of penicillin and clavulanate (a BL inhibitor), which were active against both GABHS and AGNB,(Anaerobic Gram-Negative-Bacilli) were effective in eradicating the infection. An increase in resistance of GABHS to penicillin was found when it was co-inoculated with S.aureus, Haemophilus parainfluenzae, or B.fragilis.[15]

Aerobic and anaerobic BLPB(Beta-Lactamase Producing Bacteria) might play a role in penicillin failure to eradicate GABHS tonsillitis. It was plausible that these BLPB could protect GABHS from penicillin by inactivation of the antibiotic. BLPB was recoverd in 37 of 50 tonsils (74%) removed from children who failed penicillin therapy.[16]

Strains of GABHS had been demonstrated to internalize within epithelial cells both in vitro and in vivo in recent studied.[17]

The internalization-associated gene, prtF1/stbI, had been identified more from patients with eradication failure of GABHS than had been recovered from patients with successful eradication.[18]

Since penicillin penetrate mammalian cells poorly, intracellular survival of GABHS possibly allowed the pathogens to persist despite antibiotic treatment.[19]

The intracellular spaces might therefore protect GABHS strains from penicillin that was not in high intracellular concentration. In support of this hypothesis, GABHS strains were shown to survive 4-7 days within cultured epithelial cells. Thus, internalization and intracellular survival represented a novel explanation for penicillin eradication failure.[20]

Marouni et al, compared the survival of GABHS strains from cases of eradication failure and eradication success, using an epithelial cell culture model.”Eradication failure” strains showed significantly increased intracellular survival, compared to the’ eradication success’ strains. These results demonstrated how an intracellular reservoir of GABHS may play a role in the etiology of antibiotic eradication failure.

Kaplan et al., recently examined the viability of intracellular GABHS in a human laryngeal epithelial cell line(HEp-2epithelial cell) after exposure to antibiotics (penicillin, erythromycin, azithromycin, cephalothin, and clindamycin) that were commonly recommended for GABHS. Three techniques were used to study antibiotic killing of ingested GABHS: 1) electron microscopy examination of ultra- thin sections of internalized GABHS; 2) qualitative determination of intra-epithelial cell antibiotic; and 3) special stain evaluation of intracellular GABHS viability within antibiotic-treated epithelial cells. Group A beta-hemolytic streptococci survived intracellularly despite exposure of the GABHS-infected epithelial cells to penicillin. Cephalothin (a cephalosporin) and clindamycin were more effective than penicillin in killing ingested GABHS. However, erythromycin and azithromycin, agents known to accumulate to high levels in cells, were more effective than cephalothin and clindamycin in killing ingested GABHS. These observations strongly suggest that the upper respiratory tract carrier state of GABHS results from intra-epithelial cell survival, and the failure of penicillin to kill internalized GABHS. Penicillin’s failure to eradicate GABHS from pharyngo-tonsillar tissue might be impacted by its inability to eradicate intracellular GABHS as well as its inability to maintain sufficient concentration within the tonsillar fluid. The stage of the GABHS PT (Pharyngo-Tonsillitis) inflammation determines the concentration of penicillin in tonsillar surface fluid. Stjernquist-Desatnik et al, investigated the concentration of penicillin in serum, as well as penetration to tonsillar surface fluid and saliva. Among the nine healthy subjects, despite high serum penicillin concentrations (mean, 2.04 µg/ml), there was no penetration to tonsillar surface fluid or to saliva. Of the nine patients with acute GABHS tonsillitis, eight manifested high concentrations of penicillin in tonsillar surface fluid (mean, 0.34 µg/ml) on the first day of treatment, but only two patients had penetration to the saliva. On the tenth day of treatment, penicillin was present in the tonsillar surface fluid of only one patient and was not present in the saliva of any patients. Furthermore, orrling et al., demonstrated that the cephalosporins loracarbef and clindamycin maintained higher concentration in tonsillar surface fluid for longer duration than penicillin.[21-23]

Causes of Penicillin Failure in Therapy of Gabhs Tonsillitis:

1. the presence of beta-lactamase-producing that ‘’protect’’GABHS from pencillines.[19]
2. coaggregation between GABHS and M. catarrhalis.[20]
3. absence of members of the oral bacterial flora capable of interfering with the growth of GABHS(through production of bacteriocins and/or competition on nutrients)[21-22]
4. poor penetration of penicillin into the tonsillar cells and tonsillar surface fluid (allowjng intracellular survival of GABHS.[23]
5. resistance(ie, erythromycin) or tolerance(ie, penicillin) to the antibiotic used.

6. inappropriate dose, duration of therapy, or choice of antibiotic.
7. poor compliance.
8. Reacquisition of GABHS from a contact or an object(ie, toothbrush or dental braces)[24]
9. Carrier state, not disease.[25]

MATERIALS AND METHODS

This study was conducted in the department of Microbiology, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Center, Karachi, from April 2004 to June 2005.

Inclusion Criteria: Patients of age group 5-15 years were included in this study.
Patients from government schools, OPD of National Institute of Child Health (NICH) and OPDs of JPMC and Civil hospitals of Karachi.
Children with history of sore-throat with fever were included in this study.

Exclusion Criteria: Patients with history of antibiotics since last two weeks. Patients above 15 years of age and below 5 years of age. Patients with metabolic disorders and chronic disease. Patients with history of malignancy.
250 children with suspected pharyngitis and tonsillitis and with the complain of sore throat and temperature etc attending OPDs of JPMC, Civil hospital, NICH and different govt. schools, were included in this study.
After taking all the aseptic measures, the throat swab was taken from the patients with the special care that the swab was taken from the posterior part of the pharynx and the tonsils, care was taken that the swab should not touch the tongue or cheeks, and for that purpose a tongue depressor was used. The information was recorded on a prescribed Performa. It was transported in the Amies and BHI broth.
In the laboratory the specimen was cultured and sensitivity was observed according to standard laboratory procedure.

RESULTS

Table 1: Distribution of group A, beta haemolytic streptococci in OPDs of JPMC, Civil Hospital, NICH and 20 different schools of Karachi. (n=24)

Institutions	N0. of cases	Percent
Jinnah Postgraduate Medical Centre (n=93)	12	12.9%
Civil Hospital Karachi (n=72)	06	8.4%
National Institute of Child Health (n=48)	04	8.4%
20 different schools of Karachi (n=37)	02	5.4%
Total (n=250)	**24**	**35.1%**

Table 1 shows the distribution of the GABHS in the outpatient departments of JPMC (ENT OPD) out of 93 cases 12(12.9%) were positive for GABH. In Civil hospital(ENT OPD) and in NICH from 72cases 6 cases were positive(8.4% each), in 20 different schools of Karachi out 0f 37 cases only 2 (5.4%) were positive for GABHS.

Table 2: Drug sensitivity pattern of group A beta haemolytic streptococci isolated in infected and carrier children. (n=28)

Antibiotics used	Organism isolated (Streptococcus pyogenes)			
	Sensitive		Resistant	
	No of cases	Percent	No of cases	percent
Pencillin (10units)	28	100%	0	0%
Erythromycin (15µg)	24	85.7%	04	14.3%

Table 2 shows the drug sensitivity pattern of streptococcus pyogenes isolated in infected and carrier children(28). Antibiotic discs used were Penicillin(10) units and Erythromycin(15 micrograms). The organism isolated GABHS shows 100% sensitivity to penicillin, while in case of erythromycin, it was sensitive in 24(85.7%) infected cases and resistant to 4(14.3%) cases.

DISCUSSION

Pharyngo-tonsillitis occupy a prominent place among the young children ranging from 5-15 years of age and also a most important cause of morbidity due to the post-infectious complications(suppurative and non-suppurative) produced by the Streptococcus pyogenes i.e, Aute rheumatic fever and Acute glomerulonephritis as non-suppurative and Cervical lymphadenitis, Peritonsillar or Retropharyngeal abscess, Sinusitis, Mastoiditis, Otitis media, Meningitis, Bacteremia, Endocarditis, Pneumonia as suppurative complications. And when tonsils get enlarged, they occupy and obliterate the respiratory passages.
Our way of living, over-crowding at residential places, public places and of course, at schools, the infected children cough, sneeze, laugh and handle the things and infect the other normal children. In this way the infection spreads from ill to normal.
A recent study demonstrated that over 30% of children with group A, beta hemolytic streptococci associated acute pharyngitis continued to have persistent presence of organisms in upper respiratory tract, despite the appropriate oral or intra-muscular penicillin therapy, this could be co-habitation of beta-lactamase producing normal oral flora, which "shield" Group A, beta hemolytic from penicillin, intra-cellular invasion of group A, beta hemolytic streptococci and consequent "escape" from penicillin. (shet and Kaplan, 2004)
In our study,as for as the sensitivity pattern of the organism (GABHS)is concerned, we have used two

drugs i.e, penicillin and erythromycin. And it was observed that the organism is 100% sensitive to penicillin, which was according to the other studies. As in Sao Paulo, Brazil, the group A, beta hemolytic streptococcus isolates from the infection were all susceptible to the penicillin.(data not shown) (cited by santos et al.,2003)

In another recent study carried out in Ankara, Turkey, says that because eradication of GABHS is necessary to prevent non-suppurative and suppurative sequelae, the primary outcome and antibiotic treatment goal of interest should be eradication of the bacteria(Delmar C, Bisno AL). Among the antibiotics that have been used in the treatment of GABHS tonsillitis, oral penicillin has been the firsrtline drug, and oral cephalosporinsm, macrolides and beta lactam/beta-lactamase inhibitor combinations were the alternatives. Although some reports suggested that oral cephalosporins had produced superior bacteriologic cures when compared with oral penicillin for treatment of GABHS tonsillitis, three important problems have not been resolved yet:(1) some authors believed that the difference in the cure rates might have resulted from the presence of carriers in the study groups in whom penicillin is not very effective in eradicating the streptococci from the pharynx; (2) while oral penicillin is the drug of choice in developed countries, one dose intramuscular penicillin G is the drug used most often in developing countries, the effect of which on eradication of GABHS and throat flora is not fully known;(3) Although penicillin and an alternative drug have been compared for efficacy, all of the antibiotics used for GABHS tonsillitis have rarely been evaluated in the same study.

This study further says that, the existence of BULB (beta-lactamase producing bacterias) in the throat has been mentioned as one of the reasons for treatment failure in GABHS tonsillitis treated with penicillin. some authors demonstrated a higher treatment failure if S. aureus was present in throat cultures (Simon HJ, Sakai W and Tunevail G.) The presence of BLPS (S, aureus and M.catarrhalis) was not different among the antibiotic groups in our study. they further say that, despite the low subject number in our study, it can be postulated that BL production is not as important as AHS(alpha hemolytic streptococci) in the resistance of GABHS to antibacterial therapy with oral penicillin or penicillin G.(Yildirim I, Ceyhan M, Gur D, Kaymakoglu I.)

An other study carried out by Nazgul A Omurzakova et al in Kawasaki, Japan and Bishkek, Kyrgyzstan in 2010,states that all discovered GABHS was studied for susceptibility to antibiotics, only 12.5% of GABHS positive samples out of total 80 samples were positive to penicillin. This pathogenic microbe was more sensitive to ampicillin 36.2% and to ceftriaxon 38.7% (cephalosporin). The most sensitive streptococcus pyogenes has appeared to amoxicillin 45.0%. low sensitivity has appeared to macrolids: roxitromycin 26.2% and erythromycin 23.7%.

Further more they states that, considering the recognized streptococcal etiology of rheumatic fever at present the penicillin is the drug of choice for eradication of GABHS in its initial clinical displays and for prevention of recurrence of infection. It has been established, that the treatment by phenoxymethyl penicillin during 10 days is optimum for achievement and full eradication of GABHS from throat.

In their study they further says that, in comparative randomized research it has been shown that prescription of amoxicillin/clavulanate potassium allows to amount to 100% eradication of GABHS in comparison with 70% eradication at use of penicillin ($p<0,001$). In cases of allergy to penicillin, macrolide or cephalosporin is recommended.(Nazgul A. Omurzakova et al)

An other study carried out by Michael E, Pichichero, MD et al says that there is increased acquisition of antibody to streptococcal antigens with a longer illness prior to treatment.(Bass JW, and Shvartzman P et al) This immunity has been suggested as one possible explanation for the higher success rate with penicillin in patients ill longer before therapy is started.(Pichichero ME et al) It may also be that penicillin treatment is more often successful in patients who have been ill longer prior to treatment because such patients have a greater degree of tonsillo-pharyngeal inflammation, which permits better penetration of penicillin. (Stjernquist-Desatnik A et al)

They further say that, our results and those of others (Breese BB and Spitzer TQ et al) consistently suggest that penicillin is equally effective weather administered 2,3 or 4 times daily. Although not an important factor under study conditions, poor compliance with the 3 or 4 times daily administration of penicillin may account for treatment failures in clinical practice. Less-frequent dosing improves compliance.Cockburn J and Eisen SA).

Most patients treated with penicillin for GABHS tonsillopharyngitis will experience bacteriologic eradication and a clinical cure.(Pichichero ME,Kaplan EL, Markowitz M,Shulman ST) [28].

CONCLUSION

Pharyngotonsillitis is a disease of poor community, the therapy with penicillin is economical compared with Cephalosporin group. penicillin therapy is helpful in preventing the supporative and n supporative complications caused by GABHs.

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CORRIGENDUM

It is to clarify that the Designation of Aftab Ahmed Soomro was wrongly published as Asstt. Prof. of Hematology, GMMC, Sukkur instead of his correct Designation i.e. Asstt. Prof. of Pathology, DMC, Karachi, appeared in our Journal Medical Forum Monthly, April, 2012 in Articles "Significance of Gram's stain in the diagnosis and management of Lower respiratory tract infections" (page 22) and "Cutaneous Leishmaniasis in Karachi" (page 44) (Med.Forum.Vol.23 No.4).

It is, therefore, proclaimed that the Designation of Aftab Ahmad Soomro will be read as Asstt. Prof. of Pathology, DMC, Karachi.

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