

Clinical Failure of Ceftriaxone Treatment in a Patient with penicillin Resistant Pneumococcal Meningitis

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A case of meningitis caused by penicillin resistant *Strep. pneumoniae* is described for the first time in our hospital. This case also showed treatment failure with Ceftriaxone. Patient was successfully treated with Imipenem. It is recommended that routine screening for penicillin resistance in meningeal isolates be done and in such instances, the MIC levels for third generation cephalosporins also be performed to detect resistance of any type.

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In the modern era of antibiotics, the pneumococci continue to be a major cause of pneumonia, otitis media, bacteremia and meningitis. In spite of the ready availability of inexpensive antibiotics, particularly penicillin, to which it was susceptible, the mortality rate and complications due to pneumococcal infection are increasing because of emerging resistance to penicillin.

Now that penicillin resistance is becoming widespread and even other drugs like third generation cephalosporins, are also failing to eradicate the infections, especially meningitis, the clinician is confronted with more alarming situations. In this present state, the treatment options need to be reviewed and the standard empirical treatment policies must be revised.

There are number of reports of treatment failures with third generation cephalosporins in meningeal infections caused by penicillin resistant *Strep.pneumoniae*^{1,2}. There are also reports of development of resistance to these drugs during the course of treatment².

A case of clinical failure of Ceftriaxone in the treatment of meningitis caused by relatively resistant pneumococci is reported for the first time in this hospital, and in the Eastern Province, to the best of our knowledge.

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THE CASE

An 11 months old, Saudi girl was brought to the Pediatric Emergency Room, with a complaint of intermittent fever, associated with cough, stuffy nose, and rapid labored breathing. Examination revealed a sick looking, febrile child, with temperature of 38.50C; with RR 60/minute, heart rate of 140/minute BP, 70/45 mm.Hg, moderately dehydrated, with sunken eyes and depressed anterior fontanelle. She was irritable and lethargic. Her throat was congested with cervical lymphadenopathy.

The patient was suffering from these symptoms since 7 days prior to admission. She was visiting a dispensary where she was given oral antibiotics.

An initial diagnosis of bronchopneumonia was made. The patient was admitted to the pediatric ward. CBC, ESR, Blood culture were done. Patient was started on Ampicillin 100 mg/kg BW IV 6 hourly and gentamycin 7.5 mg/kg BW IV 8 hourly.

Next day, the patient started having projectile and nonbilious vomiting. Examination showed neck stiffness along with a positive Kernig's sign. Fundus examination was normal. Lumbar puncture was done. The CSF was turbid, the cell count was 2200/mm, polymorphs 90%, lymphocytes 10%; protein 115 mg/dl and glucose 6 mg/dl³. Gram stain revealed only pus cells but no microorganisms. The latex agglutination for detecting the antigen gave a weak agglutination with Strep. pneumoniae reagent. Meanwhile, a gram stain report from the blood culture bottle revealed gram positive diplococci. The supernatant gave a positive agglutination with Strep. pneumoniae reagent in the bacterial antigen kit. A diagnosis of pneumococcal meningitis was made. The patient was started on Ceftriaxone 100mg/kg/BW/day in a single dose and dexamethasone in a dose of 1.6 mg/kg body weight in two divided doses for 4 days.

On the third day, the blood culture report showed isolation of Strep. pneumoniae. The susceptibility testing was done by disc diffusion method using 1 ug oxacillin disc for detecting penicillin resistance. The strain showed sensitivity to chloramphenicol, erythromycin, ceftriaxone, cefotaxime, piperacillin, imipenem and vancomycin. It was moderately sensitive to penicillin (10 u disc) and resistant to oxacillin 1 ug.

MIC estimation was performed in view of the penicillin resistance. The minimum inhibitory concentration for penicillin was 0.19 mcg/ml. It was interpreted as relatively resistant.

However, CSF showed no growth on the primary plates or even after enrichment. The treatment was continued with ceftriaxone initially. The fever subsided but later the patient had spiking fever along with seizures. A lumbar puncture was done again on the eighth day. CSF showed 215 cell/mm³, with protein 42 mg/dl, glucose 41 mg/dl. Gram stain revealed no microorganisms. Latex agglutination was negative. The culture did not show any growth. At the same time, CBC, ESR, blood culture and urine culture were repeated. There was leukocytosis with WBC count of 27,000/mm³ and ESR was 120 mm/1st hr. Other infective foci like otitis media and thrombophlebitis were ruled out by clinical examination. Clinically there was persistence neck rigidity and Kernig's sign. CT scan brain was done to rule out subdural effusion. All septic work up investigations including CSF examination was done in 2nd and 3rd week of illness. None gave evidence of infection elsewhere. CSF still showed the presence of pus cells and high protein.

In spite of all cultures being negative, other parameters like ESR, leukocytosis elevated body temperature indicated the presence of an infective process. As CSF findings and clinical signs supported meningeal infection, clinical failure with ceftriaxone was presumed and ceftriaxone was discontinued on the 21st day. No antibiotic was given for next two days to rule out the possibility of antibiotic fever, and the fever became continuous.

Imipenem was started on the 23rd day in a dose of 100 mg/kg BW IV 6 hourly. Fever subsided by third day after starting imipenem with residual seizures which was controlled by phenobarbitone.

The patient was discharged on the 38th day in good condition. Subsequent neurological assessment and audiometry after 4 weeks was advised. The patient was found not to have any sequelae. Phenobarbitone was discontinued after 6 months.

DISCUSSION

Following the description of the first penicillin resistant pneumococci case from Australia in 1967³, steady increase in the number of strains resistant to penicillin have been reported from other parts of the world^{1,2,4,9}. The number of antibiotics showing decreased susceptibility is also increasing^{1,4}.

Our case is the first case of PRSP meningitis to be reported from this hospital. Several case reports of pneumococcal meningitis and treatment failures with third generation cephalosporins were published from various countries. In some reports, there was demonstrable resistance in "in vitro" sensitivity testing " and in some there was no demonstrable resistance in disk diffusion tests to third generation cephalosporins, when first isolated² as in our case. Since the MIC was determined only for penicillin and could not be done for the ceftriaxone with which the patient was treated initially, it is not known whether the resistance developed during the course of treatment.

In the present case, the negative CSF smear and culture reports can be explained on the grounds of prior antibiotic therapy. The antigen could be detected by Latex agglutination test (LA test). Another possible explanation which could have been operative here is that, in experimental meningitis, in the early stage of infection, the bacteria would be more in the lateral ventricles than in the subarachnoid space or the spinal cord¹⁰. There must be minimum number of pneumococci (10⁶ CFU/ml for a positive LA test, 10⁵ micro-organisms/ml for a positive growth, 10⁶ micro-organism/ml for visualizing the organisms microscopically) for any of the parameters to be positive, this could be another factor¹¹.

The mechanism of resistance to penicillin in case of pneumococci involves the penicillin binding proteins (PBPs) which are the target for other B-lactams also^{12,13}. So it would be expected that the 3rd generation cephalosporins, also are likely to develop resistance. The bad news is that the resistance in this group will be acquired rapidly because it involves alteration of only two PBPs, in contrast to the alteration of 4 PBPs in the case of penicillin⁴.

In our patient, ceftriaxone was given for 3 weeks. In spite of this treatment the patient continued to have symptoms and signs of meningitis. When the antibiotics were withdrawn, the fever became continuous, so clinical failure was suspected.

Probable implications to be considered with the resistant strains are a doubtful potential for causing outbreaks, and whether they are associated with increased mortality. It is not known whether they have a special ability to cause outbreaks, but it would be as serious as any other outbreak of infections due to multiple resistant bacteria⁸. In one study in Spain, it was shown statistically, that there is no considerable increase in the mortality in infections caused by penicillin and third generation cephalosporin resistant strains⁵. Hence it was recommended that these drugs are still valuable in the treatment of infections other than meningitis⁵. It is not clear up to what MIC values; these antibiotics can be used for curing these infections¹³.

The treatment options in cases of penicillin resistant pneumococcal meningitis must be clearly defined. Accordingly penicillin resistance must be screened for routinely in the laboratory. By using 1 mcg oxacillin disc, penicillin resistance can be identified reliably¹⁴. The routine method of using 10U or 2U penicillin disc cannot identify intermediate sensitivity. Hence determining the MIC value is necessary. The breakpoint for the susceptible strain is <0.06 ug/ml for resistant strains > 2.0 mg and 0.1 - 1.0 ug/ml are interpreted as moderately sensitive. For the third generation cephalosporins, the routine disc diffusion tests may be misleading. Based on these clinical failures of third generations' cephalosporins in PRSP meningitis, the National Committee for Clinical Laboratory Standards (NCCLS) has amended the MIC value interpretation for these agents. The strains with a MIC of > 2 mcg/ml are now interpreted as resistant, while those with < 0.25 mcg as susceptible. The strains with MICs of 0.5 mcg-1.0 mcg/ml are considered as moderately sensitive³. A therapeutic implication of estimating MIC in meningitis is that in the experimental form the pathogens were eradicated only if the antibiotic levels in CSF exceeded the MBC

(minimum bactericidal concentration) by 8-10 fold¹⁵. When MIC values are increased, it would be expected that the required ratio may not be achieved, resulting in delayed sterilization or clinical failure.

MIC estimation used to be done by broth dilution method which was labor intensive and gave a wide concentration gradient due to doubling dilution of the antibiotic. The present method of estimating MIC is by the novel "E test"¹⁶. E test is much easier, and gives more approximate value as the concentration gradient is in continuous scale. Regarding the alternative antibiotics in such cases vancomycin is the first drug to be thought of because the mechanism of action of vancomycin is different from that of penicillin although it is also a cell wall synthesis inhibitor⁵. It is preferable to give this drug in combination with other drugs, e.g. ceftriaxone, as the levels achieved by Vancomycin in CSF are not high. Clinical failure with vancomycin alone was reported in a sickle cell patient in whom the pneumococcal septicemia progressed to pneumococcal meningitis¹³. Rifampin and ceftriaxone is another combination. Third option is increasing the dose of the ceftriaxone or cefotaxime. As this aspect is not studied well, its clinical usefulness is not clear⁹. Lastly, imipenem is another good therapeutic alternative¹¹. Though the target of action is a penicillin binding protein, the genes responsible for the resistance are not the same as those of penicillin resistance¹⁷. Meropenem another carbapenems is considered superior to imipenem not only due to lack of its epileptogenic properties, but also has excellent activity against pneumococci in vitro³.

Dexamethasone is valuable in reducing the inflammation caused by the cell wall components of pneumococci with prevention of subsequent complications, and is included in the recommended treatment protocols for meningitis¹⁸.

CONCLUSION

With increasing incidence of PRSP, there are increasing numbers of cases of treatment failures with other antibiotics as well. Hence it is recommended that routine screening for penicillin resistance pneumococci is part of the laboratory procedures. Once identified it is worthwhile estimating the MICs for penicillin and third generation cephalosporins in meningeal infections. Clear guidelines must be established for the treatment to reduce the mortality and complications.

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