The Medical Journal of Malaya
Vol. XIX, No. 1, September 1964.

SOME SEVERE ANTIBIOTIC RESISTANT STAPHYLOCOCCAL INFECTIONS IN SINGAPORE WITH SPECIAL REFERENCE TO THE USE OF AMINOSIDINE (GABBROMYCINA)

Dr. Khoo Oon Teik, M.D., M.R.C.P.E., F.R.F.P.S. and
Dr. Lee Guat Siew, M.B., B.S., M.R.C.P., M.R.C.P.E.,
Department of Clinical Medicine,
University of Singapore,
Singapore - 3.

The development of staphylococcal strains resistant to the commonly used antibiotics has been a subject of great concern all over the world. Finland (1958) pointed out that the day of staphylococcal epidemics of the order of the rampant staphylococcal pneumonia, causing 50% of deaths in the Allied Forces in World War I, might not be entirely over. This was borne out by the recurrence of staphylococcal infection in association with influenzal epidemics in 1941 and again in 1953. Shaffer (1958) stated that in 1946 widespread virulent staphylococcal infections in hospital nurseries affecting both mothers and babies was reported first in England, later in Canada, Australia, United States and finally in the rest of the world. Rountree (1958) ascribed this spread to high infectivity rather than high virulence. She reported that in Australia the spread in the community was not noticed until 1955 when there was sudden increase in the appearance of staphylococcal septicaemia caused by known hospital strains of staphylococci. She reported that a continent wide survey of all soft-tissue infections seen by doctors at their own offices in Australia showed that 45% of all these infections were due to penicillin-resistant staphylococci. Thiry-five to forty per cent were due to type 80 strains known to be the usual hospital variant. The emergence of antibiotic resistant staphylococci is attributable to the introduction of wide spectrum antibiotics. Knight (1958) observed that when new cases of staphylococcal infection were given tetracycline, a very rapid change occurred often within hours in which resistant strains replaced susceptible strains.

The choice of an antibiotic in the treatment of virulent staphylococcal infection is rendered even more difficult by cross-resistance, toxicity of drug, and wide antibiotic resistance of the organisms. Hitherto, antibiotic resistant staphylococcal infections have not constituted a major problem in Singapore but they are increasingly more evident. It would appear from literature such as mentioned above that the problem of antibiotic-resistant staphylococcal infection described in the West and Australia is just about catching up in Singapore and that the cases to be described do not comprise just a local or regional variation of the known ecology of staphylococci.

Aminosidine sulphate (Gabbromycina) is a new antibiotic discovered in the Farmitalia Research Laboratories, Milano by Canevazzi and Scotti (1959). It is a water-soluble oligosaccharide isolated from the metabolites of a strain of Streptomyces (S. Krestomyceticus n.sp.). Although it belongs to the basic antibiotic group which includes streptomcin, neomycin, viomycin, kanamycin and paromycin it differs from them in chemico-physical as well as biological characteristics. (Arcamore, Bertazzoli, Ghione and Scotti 1959). Bearing the formula $C_{23}H_{45}N_5O_{14}2H_2SO_4$, aminosidine sulphate is a white hygroscopic, water soluble powder which is fairly stable in aqueous solution and is quickly absorbed by the parenteral but not by the oral route. High level of the drug is reached in the blood when it is given parenterally, and a high concentration in the kidney is also achieved (Arcamore et al 1959). The manufacturers warn that if the antibiotic is given for long periods exceeding 10 to 15 days, toxic action on the vestibular nerves and kidneys may occur as in the case of other members of the same group, for example, streptomycin and kanamycin. This is particularly liable to result if there is renal insufficiency.

Stein (1926) in Singapore confirmed the broad spectrum of activity against gram positive and negative organisms including many resistant staphylococci. This paper records the use of aminosidine sulphate in several cases of antibiotic resistant staphylococcal infection. It is also the concern of the authors to bring to general notice the increasing incidence of such infections in Malaysia.

Results:

Table 1 shows the cases in the series. This table was prepared 2 months ago; hence follow-ups of the surviving cases have been longer than that stated in the "comments" column. Case No. 5 has since come up for review.

Table 2 shows the sensitivity to various antibiotics. Regretably Gabbromycina discs were not available for testing in all but one case.

Seven cases of severe infection, five of them proven bacteriologically due to staphylococcus aureus, have been treated with Gabbromycina. The two cases of septicaemia in which staphylococci were not cultured, were nevertheless clinically not unlike staphylococcal infections and have been included in the series. All were clinically very toxic, ill patients with high swinging fever of at least eight days duration and had had other antibiotics in full doses with no response before Gabbromycina was used. The Gabbromycina was used as intramuscular injection in dosage 0.5 Gm. 8 hourly in 5 cases and 0.25 Gm. 6 hourly in 2 cases.

In all of them the fever came under control in 2 to 3 days. During therapy transient proteinuria occurred in a few cases. In one patient, blood urea was raised temporarily.

One had a focus of infection in a pilonidal sinus and had had it excised since. Three started off as a lung infection; one probably started as a staphylococcal pyodermia.

The other two had no definite original focus of infection. One came back five months later with a brain abscess and died. Follow-up of the other cases have been from $4\frac{1}{2}$ to 10 months and they have remained well.

CASE I

Name: R.b.D. Sex: female Age: 26 years Ref: N 33231 Staphylococcal Pyodermia and Septicaemia.

Fever with septic spots 2 days. Delirious 1 day.

High swinging fever. Coma III. Multiple septic spots on skin. Spleen not palpable.

Blood cultures were negative but pus swab from skin yielded confluent growth of staphylococcusaureus.

T.W.: 13,500. P.: 85.

She was first started on crystalline penicillin 6 mega and Reverin (pyrrolidinomethyl tetracycline) 275 mg. 6 hourly. There was little response and on the 5th day, erythromycin 1G/day was used instead of the penicillin. Three days of therapy on the reverin and erythromycin combination showed no change and methicillin 4G/day took the place of reverin. In 24 hours the temperature of 101 – 104 came down to 100°F and remained so for 3 days before starting to swing again. Kanamycin 1G and erythromycin 1G/day were used for 5 days with the swinging temperature getting worse. She was then given oxytetracycline 1G, streptomycin 4G and triple sulfa 4G/day. There was temporary improvement for about 5 days only then temperature began to swing again and it was decided to use Gabbromycina. In 48 hours temperature was normal and remained normal. Then patient gradually became able to respond to questions. She received 15G Gabbromycina. On stopping Gabbromycina there was a mild fever for 48 hours but this settled spontaneously.

She was discharged 9 days after completing the Gabbromycina course, well and ambulant. At beginning of Gabbromycina course, blood urea was 40 mg.%, was 47 mg.% on 7th day, 56 mg.% on 9th day but came down to 25 mg.% before discharge. (See Fig. 1). The patient did not come back for follow-up as requested but was re-admitted almost 5 months later with symptoms and signs of a brain abscess. A right carotid arteriogram showed a large avascular region in right temporal region. At craniotomy, the brain was under greatly increased pressure. About 20 c.c.

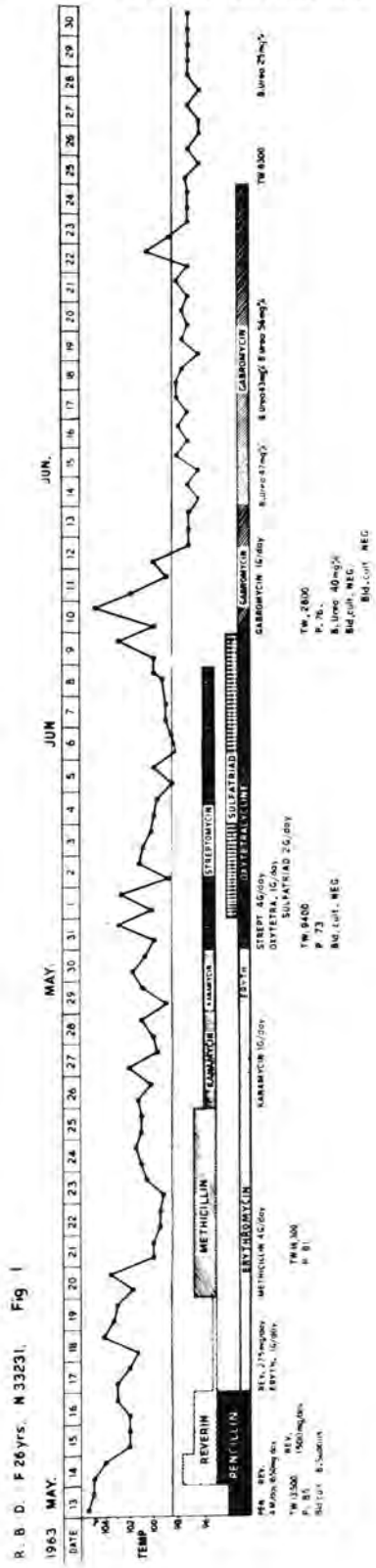
No.	Diagnosis	Other Antibiotics Used	Total Gabromycin	Blood Urea	Comments
1.	Staph. Septicaemia	Penicillin, Streptomycin, Sulphatriad, Pyrrolidinomethyl tetracycline, Oxytetracycline, Erythromycin, Kanamycin.	15G	Increased temporarily. Normal 4 days after course.	Came back 5 months later with staph. brain abscess - died.
2.	Staph. Septicaemia	Tetracycline	13G	Normal	Last seen 8 months later. Well.
3.	Lobar Pneumonia Staph. Septicaemia	Penicillin, Streptomycin, Tetracycline.	6G	Normal	Last seen 5 months later. Well.
4.	Inf. Pilonidal Sinus Staph. Septicaemia	Pyrrolidinomethyl tetracycline.	11G	Top normal (40mg.%) at end of course.	Last seen 2 weeks later. Well.
5.	Septicaemia.	Penicillin, Streptomycin.	15G	Normal	Patient has not attended for follow-up.
6.	Staph. Empyema.	Penicillin, Streptomycin, Chloramphenicol.	7G	Normal	Last seen 5 weeks later. Well.
7.	Pyogenic Arthritis with Septicaemia.	Penicillin, Streptomycin	5.5G	Normal	Just discharged from hosp. Well at discharge.

TABLE I

GABROMYCIN CASES: ANTIBIOTIC SENSITIVITY

	CASE 1		CASE 2	CASE 3	CASE 4	CASE 5	CASE 6	CASE 7
	1st Adm.	2nd Adm.						
Penicillin	-	-	-	+	-		-	
Streptomycin	+	-	-	+	±		+	
Chloramphenicol	±	-	±	+	±		+	
Tetracycline Hyd.	+	-	-	+	-		+	
Oxytetracycline	+	-	-	+	-	No	+	No
Trisulfonamide N.F.	-	-	-	-	-	positive	-	positive
Neomycin	-	-	+	±	+	culture	+	culture
Spiramycin	+	-	+	+	+	obtained	+	obtained
Kanamycin	+	-	±	++	+			
Sigmamycin	+	-	-	++	+		+	
Erythromycin	+	-	+	++	+		+	
DMC tetracycline	+	-	-	++	-		±	
Gabromycin		+++						

TABLE II



of thick yellow pus was obtained deep in temporal lobe near tentorium. The patient had been put on Gabbromycina 0.5G 8 hourly since re-admission. Staphylococcus aureus was grown from the pus, sensitive to Gabbromycina but not to any of the other antibiotics tested. The general condition of the patient remained poor and she died about 2 days after drainage of the brain abscess.

CASE II

Name: N.U.S. Sex: female Age: 31 years Ref: N 34697

Staphylococcal Pneumonia and Septicaemia.

An old case of bronchial asthma and exfoliative dermatitis, the patient was admitted with a history of 7 days scaling and soreness of skin, high fever, cough with yellow sputum and general aches. On examination she was found to be febrile, toxic looking and showed extensive exfoliative dermatitis. However, there was no weeping of skin lesions. Generalized crepitations and rhonchi were heard over lungs.

Staphylococcus aureus was grown from throat swab, sputum and blood cultures. Put on tetracycline 1G/day for 8 days she showed no response and blood cultures came back positive for staphylococcus.

Patient was then changed to Gabbromycina 250 mg. 6 hourly. Fever responded in 48 hours but was not afebrile till 10th day of Gabbromycina. She received 13G Gabbromycina. Patient was also on adrenal corticosteroids for the skin. Blood urea and urine were normal at end of course. Last seen 10 months later when patient was well — except for mild asthma.

CASE III

Name: T.S.H. Sex: male Age: 27 years Ref: N 35466

Staphylococcal Pyodermia, Lobar Pneumonia and Septicaemia. 2 days fever, and left chest pain aggravated by breathing. Signs of consolidation left lower lobe together with pleurisy. Septic spots all over chest.

Developed signs of left pleural effusion after 5 days. Staphylococcus aureus grown

from blood and pus from skin. First put on penicillin 4 mega units, streptomycin 1G and tetracycline 1G/day with no response after 7 days when changed to Gabbromycina 0.5G 8 hourly. Temperature normal after 72 hours. Received total of 6G. Blood urea normal at end of course. Last seen 7 months after course. Remains well.

CASE IV

Name: C.K.F. Sex: male Age: 26 years Ref: N 36036

Staphylococcal Septicaemia from Infected Pilonidal Sinus. 10 days ago developed boil near anus together with fever. 6 days cough with haemoptysis. 3 days chest pain, worse on breathing. Febrile and toxic. Dullness over both lung bases. Infected pilonidal sinus near anus.

Staphylococcus aureus cultured from pus from pilonidal sinus and blood. Was on reverin for 7 days with no improvement, changed over to Gabbromycina. Temperature was normal after 72 hours. Patient received 11G together. Blood urea was 20 mg.% at beginning and 40 mg.% at end of course. 2 weeks later patient was sent to Surgeons for excision of his pilonidal sinus.

CASE V

Name: T.M. Sex: female Age: 43 years Ref: N 37635

Septicaemia, ? Staphylococcal.

4 days fever and joint pains.

High swinging fever. Superficial skin abscesses over elbows, left wrist, right Tendo Achilles.

Tender red nodules over several finger tips.

Cultures taken of blood, nasal swab, sputum, urine were all negative. A high vaginal swab twice grew staphylococcal aureus but there was no local lesion seen.

T.W.: 16,000 P.: 71 E.S.R.: 125 mm./hr.

X - ray chest normal.

She was started on penicillin 4 mega/day; after 2 days streptomycin 2G a day was added. After 48 hours of this combination as temperature was still swinging she was changed over to Gabbromycina. Temperature was normal in 36 hours and the skin abscesses started clearing up. She received total of 15G. Blood urea remained normal throughout the course of Gabbromycina.

Patient last seen 4½ months later. She was well and urine was normal.

CASE VI

Name: G.L.O. Sex: male Age: 13 years Ref: N 37940

Staphylococcal Empyema.

6 days fever and pain right chest, worse on breathing. Signs of effusion right base.

Pleural tap — pus obtained.

Staphylococcal aureus grown from sputum and empyema fluid. Put on penicillin 2 mega and streptomycin ½ gm./day for 10 days with no improvement. Changed to chloramphenicol 1G and streptomycin 1G/day. Improved temporarily, then fever started swinging again.

After 9 days of chloramphenicol and streptomycin, changed to Gabbromycina 0.5G twice a day. Temperature normal after 48 hours. Given total of 7G. Last seen 3 months after Gabbromycina course, was well. Urine examination and blood urea normal at end of course.

CASE VII

Name: T.N. Sex: female Age: 59 years Ref: N 6877

Pyogenic Arthritis with Septicaemia.

Old case of rheumatoid arthritis on adrenal corticosteroid and salicylates. Developed exacerbation of joint pains associated with diarrhoea 2 days.

Swinging temperature. Toxic confusional psychosis. Both knees especially right and right elbow — signs of acute inflammation. T.W.: 13,400. P.: 80%.

Aspiration right knee joint — turbid fluid with pus cells ++. Joint fluid culture: no growth of organisms.

Started on crystalline penicillin 4 mega daily for 3 days when streptomycin 1 gm. daily

was added on because of lack of response. On 6th day changed to Gabbromycina 0.5G 8 hourly. Temperature normal in 24 hours.

Transferred to Orthopaedic Department for further management. Received total of 5.5G Gabbromycina.

At discharge on 20.5.64 patient was well and walking.

Blood urea normal throughout course of Gabbromycina.

Discussion:

Stein (1962) demonstrated in the Bacteriology Laboratory of the General Hospital, Singapore, that Gabbromycina was most effective in vitro tests against 91 strains of Proteus, E. Coli, Intermediate coli-aerogenes, Ps. aeruginosa, Str. faecalis and Staph. aureus organisms. The strains were selected at random from among those showing "considerable resistance to ordinary antibiotics in routine use." While it was effective against 24 strains of staphylococcus aureus tested as compared with 18 strains by neomycin and 20 strains by kanamycin, Gabbromycina was clearly superior at highest levels of inhibition of growth (+++) where 12 strains of staphylococcus were found to be inhibited as against 2 strains by penicillin, 1 by achromycin, 2 by neomycin and 2 by kantrex (kanamycin). On the other hand, of the 24 strains of staphylococcus aureus tested, none was insensitive to Gabbromycina, as compared with the other antibiotics. Thus 22 local strains of the 24 tested were completely insensitive to penicillin, 22 to streptomycin, 11 to chloromycetin, 23 to achromycin, 23 to terramycin, 23 to sulphatriad, 1 to neomycin, 5 to rovamycin and 3 to sigmamycin. Cocchi (1959) observed 96% of 123 strains of staphylococcus pyogeus aureus resistant to tetracycline, oleandomycin, novobiocine, erythromycin, were sensitive to aminosidine at a concentration equal to lower than 8 ug/ml. Daikos et al (1962) showed that almost all of 104 strains of staphylococcus aureus proved sensitive to as low as 2.5 ug/ml., an activity only equalled by kanamycin.

In our clinical studies, the use of Gabbromycina was restricted to those cases showing no response to the other antibiotics and the results have been gratifying. It is noteworthy that the response was fairly prompt in all cases, lysis of fever occurring within 48 to 72 hours.

All the 7 cases had a swift response to Gabbromycina after the other antibiotics had failed. Only Case I had a relapse of staphylococcal infection 5 months later. In this case a large brain abscess was found in the temporal lobe. It is very probable that the earlier course of treatment had sealed in the abscess but failure to drain the abscess in the first instance had allowed it to extend. It is interesting to note the various foci of infection in the series of cases — skin, brain, lung, pilonidal sinus, pleural cavity, joints.

Conclusion:

With the availability of Gabbromycina the physician now has a powerful antibiotic which is effective in various forms of resistant staphylococcal infection. Provided that some precaution is taken in the cases with known renal disease, no side-effects have been noticed in the present small series except transient proteinuria in one case and transient rise in blood urea in another.

REFERENCES:

1. Arcamone F., Bertazzoli C., Ghione M., Scotti T. (1959). Aminosidina: un nuovo antibiotico oligosaccaridico. 7.251.
2. Canevazzi G., Scotti T. (1959). Descrizione di uno streptomicete (Streptomyces chrestomyceticus) SP. nova produttore del nuovo antibiotico amminosidina. Giorn Microbiol., 7, 242.
3. Cocchi P. (1959). Attivita "in vitro" del 1600 F.I. su 123 ceppi di stafilococco piogene resistenti a vari antibiotici. Riv. Clin. Pediat., 64, 257.
4. Daikos G. K., Kourkoumeli P., Paradelis A. (1962). Aminosidine, a new oligosaccharide antibiotics: bacteriologic and pharmacologic observations. Antibiot. & Chemother., 12, 243.
5. Finland M. (1958). Proceedings of 6th Annual Symposium on Antibiotics. Antibiotics Annual 1958 – 1959 Medical Encyl., New York, N.Y. p. 1091.
6. Knight V. (1958). Ibid p. 1076.
7. Rountree P. M. (1958). Proceedings of the 6th Annual Symposium on Antibiotics. Antibiotics Annual 1958 – 1959. Medical Encyl. New York, N.Y. p. 1081.
8. Shaffer T. E. (1958). Ibid p. 1078.
9. Stein, J. (1962). A Note on the new antibiotic "Gabbromycina" (Aminosidine Sulphate). Singapore Med. Journ. 3, 193 – 195.