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A GUIDE FOR CONSERVATIVE THERAPY ABOARD FLEET BALLISTIC MISSILE SUBMARINES

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SUMMARY PAGE

THE PROBLEM

To prepare a guide outlining conservative medical therapy of "surgical" illness which may be encountered by medical officers serving in Fleet Ballistic Missile (FBM) submarines, emphasizing the use of antibiotic drugs, their selection, administration and contraindications.

FINDINGS

A specific and practical guide has been prepared, with useful suggestions concerning diagnostic tests and supply problems in the submarine situation. Newer concepts of massive penicillin-G therapy are detailed, and many phases of supportive therapy adapted to shipboard facilities are presented, including central venous pressure monitoring and procedures for cross-matching of blood.

APPLICATIONS

The material presented in this report should be valuable for prospective submarine medical officers and for those actively serving aboard FBM submarines where long patrols are routine and transfer of personnel to Naval hospital facilities is impossible without aborting the submarine's mission.

ADMINISTRATIVE INFORMATION

This report was prepared by the author in partial satisfaction of the requirements for qualification as a Submarine Medical Officer. Having been accepted as a Qualification Thesis, the manuscript has been recommended for publication as a Submarine Medical Center report, in order to make the information available in the Technical Library and for use in the classes at the School of Submarine Medicine. It has been designated as Special Report No. 67-12, under date of 11 October 1967.

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ABSTRACT

A guide for conservative, medical therapy of "surgical" illness aboard FBM submarines is presented. Emphasis is placed on antibiotic drugs -- their selection, administration, and contraindications. Newer concepts of "massive" penicillin G therapy are detailed. Phases of supportive therapy adapted to shipboard facilities include central venous pressure monitoring and a procedure for cross-matching blood. The epidemiology, detection, and treatment of penicillin allergic reactions are outlined. The paper concludes with practical suggestions concerning diagnostic tests and supply problems.

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A GUIDE FOR CONSERVATIVE THERAPY ABOARD FLEET BALLISTIC MISSILE SUBMARINES

INTRODUCTION

Submarine Medicine is a significant asset supporting Fleet Ballistic Missile (FBM) submarines routinely deployed on prolonged submergence missions. The goal of the Submarine Medical Officer is to insure that no operational commitment need be interrupted for medical reasons.

This paper contains recommendations for specific treatment modalities useful in the conservative therapy of severe "surgical" illnesses that may occur at sea. The rationale of a conservative medical approach as detailed by Rice (1) needs no repetition here. Each Medical Officer, however, must appreciate the necessity of extensive planning and preparation. He is solely responsible for having aboard adequate diagnostic aids, drugs, and treatment supplies. Each Medical Officer will find it necessary to supplement the Initial Outfitting List according to his own particular capabilities.

The information that follows should be helpful in that planning. Difficult management situations are presented in a generalized manner. Certain aspects of conservative therapy, infrequently practiced ashore, are presented in detail. These suggestions are not recommended as dogma but rather as a frame of reference within which individual Medical Officers may plan their own actions.

ORGINS OF PATHOLOGY

Preventive medicine deserves first priority in the practice of Submarine Medicine. Thorough, conscientious screening ashore will detect most medical problems prior to patrol.

Medical problems arising after deployment are generally limited to infectious disease, exacerbations of chronic non-disqualifying conditions, de novo abdominal "surgical" conditions, or trauma. Preventive measures include scrupulous shipboard sanitation, careful environment control, and an effective shipboard safety program. Completed dental care prior to each deployment virtually eliminates dental problems requiring unusual attention.

The predominant infectious disease encountered is upper respiratory disease. Although acute respiratory disease (ARD) is innocuous, the fatigue and stress met in the pre-deployment period contribute to progression in some men to lower respiratory infections which become severe in the time period just prior to deployment. It is a worrisome decision to begin a patrol with one or more cases of mild pneumonitis aboard. The Medical Officer is asked to balance the operational value of these men, who for practical purposes cannot be replaced on such short notice, against the remote possibility of complication such as pulmonary abscess. Mild respiratory infections often precede acute appendicitis or mesenteric adenitis by several days to four weeks. Theoretically then, outbreaks of ARD prior to deployment might slightly increase the probability of occurrence of those acute abdominal episodes while on patrol. Whether dealing with a complicated lower respiratory infection or abdominal inflammation, the pathology to receive primary attention is bacterial infection with priority also given to possible fluid imbalance.

Another pathologic condition is clearly aggravated by the stresses of pre-deployment and of patrol. The propensity of many persons to react to stress with gastric hyperacidity is a normal expectation. Since disqualification standards are realistic on this point and require symptoms and signs of actual ulceration, the risk of misjudging situational reactive hyperacidity is always present. Should ulceration occur and hemorrhage follow, the primary management problems will be depleted blood volume, and, in case of perforation, a risk of septic peritonitis. Evidence to substantiate that risk will be presented.

Traumatic pathology of particular interest in this discussion could arise from extremely rare mechanical failures, explosion, or from the relatively common falls from ladders or through hatches. Injuries of the head or of the viscera compound the problems of blood volume maintenance and control of infection with the threat of severe anatomic dysfunction such as intracranial hemorrhage, organ prolapse, or ruptured viscus.

BACTERIA INVOLVED IN SPECIFIC INFECTIONS

Control of infection is applicable in each class of pathology mentioned. Whether infection has been acquired via the respiratory route, introduced by rupture of the cranial vault, ocular penetration, or perforation of a viscus, therapy must be directed toward long-term recovery. Since bacteriologic verification of original organisms or of therapeutic effect is not available,

choice of therapy will usually be arbitrary and must be effective without later modification based on laboratory results.

The agents of bacterial infection are those species composing the normal flora of the organ system proximal to the side of lost integrity, where invasion can be expected to occur. Invasion of the central nervous system (secondary bacterial meningitis) following certain facial bone trauma is accomplished by gram-positive organisms including H. influenza, pneumococci, relatively avirulent staphlococci, and streptococci listed in decreasing order of incidence (2). A less likely secondarily infecting organism is N. meningitis. All these organisms reside in both nasopharyngeal and sinus cavities.

In individuals with lower respiratory infection complicated by superinfection or pulmonary abscess, the best guide to the predominant organism will be the past history and a current gram stain of the sputum. Since recent antibiotic therapy will have been employed in most cases, the likelihood of drug resistant strains may limit choice of therapy in a situation where the number of drugs available is already relatively small.

The most threatening microbial populations encountered are the normal flora of the intestinal tract. Those organisms resident in the bowel from the ilium to the rectum are listed in Table I (3). The nature of the bacterial flora of the remaining small intestine has been disputed in the literature. Recent investigations, however, indicate the presence of A. aerogens and E. coli in 17% of jejunal aspirates when sampled by intubation (3). When sampled by needle aspiration at laparotomy, 80% of jejunal specimens, and 72% of ileal aspirates contained streptococci or coliforms (4). The contents of the stomach and proximal portion of the duodenum reflect oropharyngeal flora being swallowed and then gradually inactivated by gastric secretions. Antibiotic therapy of mixed infections with such organisms has received much clinical attention.

A pertinent clinical series reports twenty-one cases of esophageal perforation treated only with intubation, intra-venous fluids, and antibiotics. Mortality (5%) is less than that reported in surgically treated series. Fever persists in these patients for about seven days and drugs are continued for several days more. Nevertheless, the success of conservative treatment (ten million units penicillin i.v., and one gram streptomycin i.m. per day) is reflected by reduced mortality in the long run (5).

APPROPRIATE ANTIBIOTIC THERAPY

Systemic antibiotic therapy is necessary in each of the situations described. Choice of drug is based upon the types of organisms expected and the patient's drug tolerance. Dose should be as high as is feasible early in therapy in order to minimize emergence of resistant strains.

Attempts should be made to avoid concurrent therapy with drugs which are known to have antagonistic antimicrobial modes of action. For example, concurrent use of penicillin and tetracycline preparations is not usually recommended. The bacteriocidal action of penicillin is related to growth and multiplication of daughter bacterial cells having defective or absent cell walls with subsequent osmotic lysis. Tetracycline, a protein synthesis inhibitor, slows the growth rate of a population of susceptible microorganisms thus reducing the opportunity for expression of the bacteriocidal property of penicillin.

Certain major drugs are central to the treatment of severe infections. The most useful drugs are streptomycin, kanamycin or chloromycetin, and the various forms of penicillin.

The Penicillin Family:

Specific penicillin allergy is seen in two to seven per cent of patients (6). For patients not allergic to it, penicillin is the least toxic antibiotic yet developed. For parenteral treatment of most gram-positive organisms, penicillin G is the most potent preparation, gram for gram, of all penicillin derivatives. This is also the least expensive form of the drug, a consideration leading to massive dosage therapy which can suppress a wider spectrum of organisms. Oral therapy of lesser infections is best performed with penicillin V which is reliably absorbed from the gastrointestinal tract.

The likelihood of penicillinase producing organisms presenting in the submarine situation is considered to be far less than in the hospital populations reported in the literature. Of the postulated situations, however, one complication of previously treated pneumonitis including pulmonary abscess might well present such a problem. Those penicillins active against penicillinase-producing staphlococci are methicillin, oxacillin, nafcillin, and cloxacillin. Methicillin can now be considered obsolete due to its relatively low potency (dose range 10-12 grams per day i.v.). Oxacillin or nafcillin used parenterally are now the drugs of choice (4-6 grams per day i.v. or i.m.). When oral therapy is indicated, as in the follow-up phase of treatment with parenteral oxacillin, cloxacillin or dicloxacillin should be chosen since they are

absorbed twice as well as oral oxacillin (7, 8). Nafcillin has exhibited irregular gastrointestinal absorption (9, 10) and is the least desirable of the three drugs in its oral form.

When penicillinase producers are unlikely and mixed infections are being treated, ampicillin should be considered first drug of choice. Unlike the other penicillin derivatives, ampicillin retains most of the potency of penicillin G while having a new, wide spectrum of action not available with previous penicillins. As in the case of parenteral oxacillin therapy, oral therapy with ampicillin should be maintained for two weeks following the acute treatment situation. Those organisms which are inhibited by ampicillin therapy are H. influenza, Strep. viridans, E. coli, Aerobacter, Alkaligenes fecalis, Proteus mirabilis, Salmonella, and Shigella. Special notice should be taken of high activity against enterococci (11). In case parenteral ampicillin is not available, crystalline penicillin G in doses not less than ten million units per day should be utilized. Newer concepts of massive penicillin G therapy (40-70 million units per day) as a single therapeutic agent are discussed in a separate section which follows.

For those patients known to be allergic to penicillins, consideration may be given to lincomycin which is discussed below. Hyposensitization to penicillin has been successful in emergencies. One method is presented in a following section.

Drugs Useful in Gram-Negative Infections:

The principal agents useful in combating severe gram-negative infections, as recommended by Rice (1), are streptomycin and chloromycetin. Other recent authors recommend kanamycin (12, 13, 14). The effectiveness and toxicity of these drugs is discussed below.

Streptomycin therapy has caused vestibular damage and auditory loss. These effects, carefully documented in tuberculous patients, appear to be directly related to total cumulative dose administered. At dose levels of three grams per day, vestibular damage was regularly seen after three weeks. At lower doses, damage was evident in four to six weeks (15). Therefore, intramuscular doses of one gram each twelve hours for seven to ten days seem justified. Moreover, the probability of synergistic effect with penicillin continues to be documented (16).

Chloromycetin (chloramphenicol) is the most potent broad spectrum antibiotic available. It is not effective against many strains of Strep. fecalis,

Corynebacteria, or Clostridia and is almost completely ineffective against Pseudomonas aeruginosa (17). It exerts a profound inhibition on protein synthesis in other common pathogens. In combination with penicillin and streptomycin, chloromycetin has been the drug of choice for gram-negative sepsis by many writers in the recent literature. Newer combinations recommended include ampicillin in order to inhibit entercocci as well. Although chloromycetin toxicity has possibly been overemphasized, that factor is sufficient to reserve chloromycetin as a drug of last resort in most clinical situations. A complete blood count should be performed after each forty-eight hours of therapy, with therapy stopped if the total white count drops below 4,000 per cubic millimeter or a progressive drop in hematocrit is observed (19).

Kanamcyin is now recommended by some writers as the drug of choice in gram-negative sepsis following clinical trials of more than eight years that have defined its toxicity (13, 14). Kanamycin has been found free of permanent nephrotoxicity when used in the recommended dose range in all patients not already in severe renal failure. Irreversible ototoxicity, observed in early clinical trials, is now reported to be infrequent (14). Kanamycin is a bacteriocidal drug in higher concentrations (20). It is highly active in vitro against Kl. pneumonia, E. coli and A. aerogenes. It is moderately active against Straph. aureus and Proteus species (83% and 81% of strains sensitive respectively) (14). Intraperitoneal use of this drug in cases of generalized peritonitis has yielded good results (14). Studies with other antibiotics in patients undergoing peritoneal dialysis indicate a relatively poor movement of drug between the blood serum and peritoneal fluid (21, 22). Such work may explain the success of intraperitoneal kanamycin, although that drug obviously could not be tested in the clinical situation cited. Intraperitoneal administration may "sterilize" the source of organisms invading the blood stream, while intramuscular drug treats the septicemia.

Drugs with Specific Uses:

Certain drugs related to the postulated therapy situations may be considered optional in our current consideration. One or more of these must be chosen by the Medical Officer in his plans to treat patients who may be allergic to the major drugs discussed or to treat superinfection if encountered.

Cephalothin is available for wide spectrum therapy and enjoys freedom from allergic complications in patients with a history of penicillin allergy (23). Cephalothin, however, is a relatively low-potency drug, presents problems of administration (24), and does not possess enough unique properties to merit routine stocking as a medical supply in the submarine situation.

This judgment is partly based on the availability of lincomycin which, in limited clinical experience, has displayed most of the capabilities of cephalothin in gram-positive infections, and has the added advantages of higher potency and lower cost (25). It is still too early to recommend lincomycin as the first drug of choice in patients allergic to penicillin, but sufficient clinical evidence should accumulate in the literature in the near future to aid in making this choice.* Lincomycin is active against Staph. aureus (regardless of penicillinase production), Strep. pyogenes and viridans, and Diplococcus pneumoniae. Until more clinical evidence is reported for this drug as a substitute for penicillin, Medical Officers may wish to carry an adequate stock of parenteral erythromycin to treat at least one patient through an acute episode at sea. It must be remembered that only the most stoic patient can tolerate intramuscular or intravenous therapy with erythromycin (26). Avoid simultaneous administration of lincomycin and erythromycin. An antagonistic action of these two drugs to Staph. aureus has been clearly shown in vitro (27).

A final recommendation as to the composition of the basic essential antibiotic inventory is made to counter the most feared superinfecting organism following peritonitis, severe burns, or massive antibiotic therapy--Pseudomonas aeruginosa. Although massive doses of penicillin G or chloromycetin have inhibited some strains of Pseudomonas, the drug of choice is colistin (11, 28). Colistin is often highly toxic, and adequate renal function must be evident before the drug can be applied. It is recommended that a supply of colistin be carried to be used as a last resort when the clinical course is suggestive of Pseudomonas superinfection. The recommended dose is 150 mgm each twelve hours i.m. (reference 11) or 2.0 mgm per kilogram each twelve hours i.v. (reference 29).

Several of the serious management situations postulated earlier in this paper can be treated as gram-negative sepsis. Similar ogranisms are likely to be involved, and lack of bacteriologic facilities limits narrower, more precise therapy in the long run. Two classes of drugs classically considered

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* Benner, E. and Northland, V.: Methicillin-Resistant Staphlococcus Aereus Antibimicrobial Susceptibility, New England J. Med., 277:678-680, 1967. In virto studies of twenty-two strains of Staph. aureus shown to be resistant to methicillin showed uniform sensitivity to vanocomycin, lincomycin, and cephalothin. Since vanocomycin is still considered to be a relatively exotic drug, unlikely to be available to Submarine Medical Officers, the choice of lincomycin in this situation seems justified.

in such treatment now appear to be replaced by more potent or more specific agents. Both tetracyclines and sulfas are conspicuous by their absence from discussions of therapy of severe infections. Ampicillin has become the drug of choice for H. influenza infections, and sulfa can no longer be recommended for treatment of meningococcal infection. The tetracyclines still have a place in specific infections (Eaton agent pneumonitis, urinary tract infection) amenable to oral therapy, but parenteral use has been replaced by other agents of higher potency and clouded by reports of hepatic and renal toxicity (30, 31, 32). Therefore, in this consideration of treatment of severe infections in the submarine situation, tetracyclines or sulfas have not been recommended.

In summary, utilization of certain essential antibiotics has been discussed, and alternative drugs of choice have been mentioned. A basic, minimum inventory should include parenteral dosage forms of kanamycin, streptomycin, crystalline penicillin G, ampicillin, chloromycetin and colistin, as well as at least one parenteral drug active against penicillinase producing organisms.

Massive Penicillin Therapy:

Recent evidence in the literature supports application of crystalline penicillin G to treatment of infections with organisms generally considered to be resistant to penicillin. In high dose ranges, penicillin G suppresses a wide spectrum of organisms including many strains of gram-negative normal flora.

In an early report, Weinstein et al (33) present extensive data on serum levels attained with "massive" therapy regimes in seventeen patients considered failures after standard therapy. Penicillin G was administered rapidly i.v. every six hours in individual doses in three ranges: less than five million units, five to ten million units, and twenty million units. Thirteen out of seventeen patients received forty million or more units of penicillin each twenty-four hours for ten to fourteen days.

Tube dilution sensitivity studies for the corresponding serum levels are reported for 240 strains (including 221 from fresh clinical specimens) encompassing nine species of gram-negative bacteria. From tabulated data, it is clear that serum levels attained in the middle range of therapy (156-625 units per ml serum) are nearly as effective in vitro as the highest range (1500-2000 units per ml serum). Middle range serum levels inhibited in vitro growth of the following percentages of strains tested in six gram-negative groups.

Organism	Strains Sensitive
Aerobacter aerogenes	75%
Alcaligenes faecalis	80%
Escherichia coli	94%
Salmonella (var.)	92%
Shigella (var.)	100%
Proteus Mirabilis	100%

Clinical results in the seventeen problem patients tend to support the in vitro data. Thirteen bacteriologic "cures" resulted, and three patients showed "significant responses." Some useful clinical notes are included. Younger patients tend to lose their serum levels of drug faster than older patients. This may support a recommendation for maximum dose in the submarine population under consideration. The potassium content of crystalline penicillin G is 1.5 milli-equivalents per million units of drug. In spite of this, no potassium intoxication was detected in the series reported. Mild central nervous system effects were seen in two patients with predisposing causes (uremia). The authors recommend a single dose of ten million units in cases of complete renal failure. Other observers (25) have reported similar mild seizure-like effects in patients with severe renal failure.

Recommended Therapy of Gram-Negative Sepsis:

In a more recent article, based upon additional clinical experience, Weinstein and Klainer (28) present the following recommendations for treatment of septic shock. The recommendations are made with the comment that the responsible organism is generally not known during the early, crucial phase of treatment. Their recommended treatment: Streptomycin, 1.0 gm/day (i.m.); chloromycetin, 4.0 to 6.0 gm/day (i.v.); penicillin G, 40-60 million units/day in divided doses (i.v.) every four to six hours. Support of blood pressure only to a level of 35 to 40 mm Hg is recommended using metaraminol (Aramine).

In view of recent favorable reports on the use of kanamycin, it may be wise to substitute this drug for chloromycetin for the first phase of treatment, and then to add chloromycetin on the third or fourth day if significant improvement has not resulted. Maximum recommended dose of kanamycin is 500 mgm (i.m.) every six hours for forty-eight hours, then 500 mgm each twelve hours for four to five days thereafter. In 228 patients with severe gram-negative infections treated with kanamycin, mortality was 9.5% as compared with 37-55% cited in other large series (13).

Suggested therapeutic combinations for mixed infections involving gram-negative organisms are:

(a) Ampicillin 50 mgm/kg for 48 hours; then 25 mgm/kg i.v.
Kanamycin 0.500 gm q 6 h for 48 hours; then 0.250 gm q 6 h for six days i.m.
Streptomycin 1.0 gm q 12 h for minimum of five days i.m.

With addition of Chloromycetin 4-6 gm/day i.m. or i.v. if significant improvement is not noted after 48 hours.

Kanamycin may also be administered intraperitoneally in cases of peritonitis.

(b) Crystalline Penicillin G 10,000,000 units q 6 h i.v.
Streptomycin 1.0 gm q 12 h i.m.

Kanamycin or Chloromycetin may be added as in (a).

SUPPORTIVE THERAPY

Although emphasis has been placed on antibiotic therapy, the success of conservative therapy depends on excellent supportive care. The classic article by Rice remains the best primary guide in the submarine situation (1). Simulation of hospital bedside care may require considerable ingenuity aboard ship. Many helpful devices are illustrated in the Manual of the Hospital Corps which is regularly updated by the Hospitalman aboard.

Location of Shipboard Treatment:

Selection of treatment site aboard ship should be made with consideration for patient privacy and adequate working space. For acute, severe cases, the Executive Officer's stateroom may be the most appropriate choice. Consider proximity of electrical outlets, wash basins, and a head. If patient isolation for contagious disease is at issue, the same area may be appropriate.

Nasogastric Suction:

In several serious management problems, placement of a nasogastric tube is an important early step. Decompression is the most common indication encountered in abdominal problems, but prevention of vomiting followed by aspiration may be necessary in many cases of trauma. Lumen diameter of

tubes carried aboard should be of adequate calibre (#18 French) to assure efficient operation without demanding continuous attention or irrigation. The fallibility of suction apparatus suggests regular checks for presence of vacuum in the receiving bottle and periodic irrigation of the nasogastric tube with ten to twenty cubic centimeters of fluid. As a back-up, the two-bottle gravity suction device, illustrated in the Manual of the Hospital Corps, can be assembled on board.

Fluid Balance:

Careful intake and output records will be helpful in most cases. The use of indwelling catheters, however, should be avoided in the shipboard situation unless absolutely necessary. Condom catheters will serve most needs.

Intravenous fluids are well provided in initial outfitting. Administration, however, often requires innovation. Bottle hangers must be contrived and tubing extension sets (not provided) are most useful. Placing intravenous needles peripherally in the hand or wrist prior to use of antecubital veins is recommended. Ankle veins should be reserved for cutdowns. For long term i.v. therapy, the use of 20-gauge thinwall pediatric scalp vein sets in the hand or wrist can be most convenient and may free the patient from the restrictions of an armboard. The use of intravenous catheters is attended with well known rare occurrences of breakage and loss of a catheter segment into the vessel. Only the Medical Officer who has personally placed such devices many times should undertake to use them aboard ship.

Central Venous Pressure:

In those severe management cases where fluids are administered for true blood volume or cell mass depletion rather than as simple fluid maintenance or as a vehicle for drugs, serious consideration should be given to monitoring central venous pressure. A method extensively utilized at the Oak Knoll Naval Hospital includes a sterile pediatric feeding tube inserted through a suitable antecubital vein and passed to a point (calculated by external measurement of the patient) judged to be near the atrium. The tube is connected via sterile three-way stopcock to a slow saline infusion and a lumbar puncture set manometer. With the stopcock at the level of the mid-axillary line, venous pressure from eight to fourteen centimeters of water is considered normal. These indications are also used by Weinstein and Klainer (28). Administration of no drugs or potassium-ion-containing compounds should be made through the central venous monitoring catheter.

In the event whole blood transfusion becomes necessary, an emergency major cross match should be performed. In the acute situation, physiological saline solution maintains blood volume adequately, and plasma expanders are available to allow additional time for the extremely important protection of a cross match. An appropriate procedure for emergency major cross matching adapted to shipboard requirements is detailed below.

Shipboard Cross Matching of Blood.

The rare occasion for whole blood administration requires advance training and rehearsal for most Medical Officers. One administrative detail easily overlooked on medical records is complete blood-typing of each crew member. Records of Rh type as well as major ABO blood group will greatly simplify the choice of donors in the midst of an emergency situation. Screening for any history of jaundice in donors must be adhered to. Retyping the patient and prospective donors is a rapid procedure, and may save valuable time and materials in the event of an error in medical record entries.

Emergency cross matching can be limited to two tests, the major cross match between recipient serum and donor cells and the same cross match adding bovine albumin to the suspension. Using small test tubes rather than depression slides allows water bath incubation which is considered invaluable in detecting low titre incompatibilities. The rotor cups of the standard urinalysis centrifuge can be made to support small cross matching test tubes by inserting wooden blanks in the cups so that the test tubes can be removed with ease.

Two drops of recipient serum are added to each of four test tubes labeled A, B, C, and D. Two drops of 22% or 30% bovine albumin are added to tubes C and D. Using a clean wooden stick, small amounts of cells from clotted donor blood are added to each test tube. Proper cell numbers (approximately 2%), yield a pink translucent suspension. Too few cells are difficult to assess upon inspection for agglutination, and a too heavy suspension can obscure incompatibilities by exhausting available antibodies from the recipient serum sample.

All tubes are centrifuged until a cell "button" forms in the bottom of the tubes (approximately one minute at 1,000 rpm). Tubes A and C are gently agitated by light taps with a finger. They are then placed in water adjusted to about 37°C. Tubes B and D are gently agitated, then poured on clean microscope slides and examined under low power. Detection of clumps of as few as three or four red blood cells is evidence of major incompatibility.

White cells should not be confused with clumps. Hemolysis has the same significance in indicating incompatibility as agglutination. Of course, gross agglutination evident in test tubes would make closer inspection unnecessary, but a majority of incompatibilities will be seen only under magnification. Following 37°C water incubation of twenty to thirty minutes, tubes A and C are again centrifuged. They are then examined in the same manner as the previous tubes.

"Incompatibilities due to the important anti-A and anti-B antibodies will be detected in the serum cross match after direct centrifugation. Incubation or addition of albumin will weaken the reaction of these antibodies. The same is true of the majority of other specific blood group antibodies of the 'cold' variety. The serum albumin test is a sensitive test for Rh antibodies. The direct centrifugation is carried out with the purpose of detecting Rh antibodies in high titres and presenting the prozone phenomenom. The incubation followed by centrifugation will detect Rh antibodies present in low titres." (Quoted from reference 34).

If time permits, elaboration of the above procedure utilizing the Coombs Test is recommended. Coombs reagent (anti-human-globulin: two drops) is added to an incubated major cross match tube (like A or B) after three washings of the cells by saline addition, centrifugation, and decanting. The resulting Coombs-washed cell suspension is centrifuged without delay and examined for agglutination. A minor cross-match using donor serum and patient cells can be done repeating the procedures of a major cross match, but is of limited importance and is optional. (The above procedures adapted from reference 34).

PENICILLIN ALLERGY AT SEA

A possible dilemma in any severe infection is a history of penicillin allergy in the situation where penicillin is clearly the drug of choice. The hazard of severe complications would seem to be even more significant in the isolated submerged situation. To aid in making appropriate decisions, the following definitions of reactions, information about skin tests screening reliability, and method of hyposensitization is presented.

Definition:

Types of penicillin allergy are quoted from reference 36. "Immediate allergic reactions begin within three to twenty minutes after administration

of penicillin. They are manifested by diffuse urticaria, pruritus, asthma and rhinitis, hypotension and shock, and laryngeal edema, or combinations of these conditions. Anaphylactic reactions are life-threatening immediate allergic reactions.

"Accelerated allergic reactions begin between one hour and forty-eight hours after the administration of penicillin and consist mainly of diffuse urticaria or pruritus.

"Late allergic reactions to penicillin begin three days to two weeks after the administration of penicillin. They are manifested by diffuse rashes (urticarial, maculopapular, erythemas), and occasionally accompanied by fever, arthralgias, and other signs, termed 'serum-sickness-like reactions.' Other less common clinical forms of penicillin allergy also exist, i.e., local allergic reactions, hemolytic reactions, allergic contact dermatitis, etc."

Detection:

Estimates of the frequency of allergic reactions to penicillin range from one per cent to ten per cent. The lower figure is probably closer to the actual incidence in a general, ambulatory population, and the higher figure is probably applicable to select groups, such as the chronically ill who have been exposed repeatedly to penicillin, and hospitalized patients with serious acute bacterial infections (37).

Although skin-testing has been proved fallible in some instances, a negative skin test in 68 out of 80 patients with histories of penicillin allergy was followed with successful penicillin treatment without subsequent immediate allergic reaction. One patient had a late allergic reaction (36). The same author recommends use of crystalline penicillin G for skin testing when more sophisticated materials, like the benzylpenicilloyl-polylysines, are not available.

Drug Hyposensitization:

If penicillin treatment is deemed essential, even in the presence of established allergy to the drug, hyposensitization as the beginning phase of therapy can be performed, but the very great risk of this decision in the submarine situation must be realized. For reference, a schedule of hyposensitization to crystalline penicillin G is presented in Table II. If therapy is interrupted, the hyposensitization schedule must be repeated (38).

Treatment of Severe Allergic Reactions:

Treatment of severe sequellae of drug allergy is well known. The use of epinephrine and anti-histamines generally must be supplemented by parenteral steroid therapy or even the administration of ACTH as a depot "gel" preparation or, as favored by some clinicians, as an aqueous intravenous infusion.

DIAGNOSTIC NOTES

One tenet of successful conservative therapy is a reasonably accurate clinical diagnosis. The Medical Officer has diagnostic techniques available to him that may have fallen into disuse since his medical student days.

A reliable, reproducible white blood-count may depend on counting additional chambers. An accurate differential blood count will be easier with fresh staining materials and occasional practice. Detecting continuing blood losses over several hours of internal hemorrhage is impractical with the Sahli hemoglobinometer. The acquisition of a microhematocrit centrifuge is worthwhile due to the speed, reliability, and precision of information from this method.

In cases of infection, the best objective evidence available may result from a gram stain of clinical material. Careful records of body temperature will be a primary indication establishing duration of therapy.

In cases of possible intraperitoneal hemorrhage or infection, a cautious four quadrant tap with standard syringe and lumbar puncture needle can provide definitive evidence.

Cardiac rate monitoring can be jury-rigged using electronic test equipment available aboard ship. Skin voltages are adequate to deflect a standard oscilloscope without preamplification.

It is now technically feasible to provide a shipboard X-ray capability which could be most useful in some diagnostic situations such as persistent pneumonitis, pneumothorax, carditis, intestinal obstruction, or certain cases of trauma. Utilizing transitorized equipment, designed for field survey work, and polaroid film, radiation hazards should be minimized and a new dimension added to the diagnostic accuracy.

SUPPLY CONSIDERATIONS

It is a good policy for the Medical Officer to pay close attention to the details of procuring medical supplies. In order to stay within fiscal allotment guidelines, careful records of materials actually received are essential. Some items will be required to be "open purchased", and success in actually receiving such items often depends on the accuracy of data (description, manufacturer, quantity) provided on your requisition. Obtain data before departing for an advanced base where requisitions are actually prepared. Sources of such information are more difficult to locate at advanced bases.

Well in advance of deployment, the Medical Officer should consult his Commanding Officer concerning the strategic situation in the planned patrol area, the realistic possibilities of patient transfer, and the expected elapsed time between a decision to transfer a patient and the transfer itself. Armed with this intelligence, quantitative estimates of necessary supplies will be possible.

Antibiotics can consume a large portion of available funds since they have a limited shelf life yet have a high unit cost. Keep a running inventory of all items which have expiration dates. Some ships have arranged to trade antibiotics with only four to six months of shelf life remaining for fresher material from medical activities ashore, such as U.S. Naval Hospitals, which have a high utilization rate and can assure that the drugs will not be wasted. Drug storage conditions aboard nuclear submarines are nearly ideal; this fact is a useful argument when negotiating a trade.

The form in which a drug is supplied can influence your selection. The preparation of streptomycin most commonly used in hospitals is a suspension supplied in injectable (Tubex) form. Maximum shelf life is eighteen months, and after the usual delays of the supply system, less than twelve months may remain at the time of receipt. The crystalline form, however, available in the stock system, is less expensive and has a shelf life of sixty months. Storage space is at a premium, and in view of the central role of crystalline penicillin G in medical planning, the open purchase of hospital stock vials containing twenty to thirty million units is recommended. These allow rapid, sterile reconstitution of large doses in contrast to the one million unit vials available through the stock system.

The separate inventory of "perishable" items can also include vaccines, blood typing serum, atmospheric contaminant testing tubes, certain diagnostic test reagents, and radiation monitoring supplies. Other items which should be rotated regularly are Wright's stain, crystal violet from the gram stain set,

and carbol fuchsin stain if you are prepared to examine for acid fast organisms.

The last drug type mentioned in this paper which may need to be increased on board after initial outfitting is a parenteral steroid (e.g. prednisone) and/or ACTH as discussed under treatment of severe allergic reactions to drugs. It is understood that individual preferences will be quite varied in this selection.

Equipment is well supplied with the exception of a micro-hematocrit centrifuge which can be ordered through the supply system at very low cost. Consider acquiring disposable devices as they appear on the stock listings. Most are compact and have multiple possible uses.

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TABLE I

Normal Flora of Colon and Ileum

*Streptococci
  *alpha
  *beta hemolytic
  *gamma

Staphlococci

Bacillus (species)

*Aerobacter aerogenes

*E. coli (I and II)

E. freudii

Alkaligenes (species)

Neisseria

Salmonella (species)

*Bacteroides

*Lactobacillus

Clostridia

Diptheroids

* Found in more than twenty per cent of cases, (Reference 3)

TABLE II

Hyposensitization Method Used in Patient with Endocarditis

Date and Hour	Sensitive to Penicillin Units of Penicillin	Route
1/29/65		
1100	1	ID
1130	5	SC
1200	10	SC
1230	20	SC
1300	40	SC
1330	80	SC
1400	100	SC
1430	150	SC
1500	200	SC
1530	300	SC
1600	500	SC
1630	800	SC
1700	1,000	IM
1730	2,000	IM
1800	4,000	IM
1830	6,000	IM
1900	8,000	IM
2000	10,000	IM
2100	11,000	IM
2200	12,000	IM
2300	13,000	IM
2400	14,000	IM
1/30/65		
0100	15,000	IM
0200	16,000	IM
0300	17,000	IM
0400	18,000	IM
0500	19,000	IM
0600	20,000	IM
0700	20,000	IM
0800	20,000	IM
0900	50,000	IM
1000	100,000	IM
1100	10,000,000	IV (Start)
1/31/65		
0800	20,000,000	IV (Start)
2/1/65		
0800	50,000,000	IV (Start)

Note: Two oral antihistamines administered throughout schedule. No local or general reactions observed. B.P. normal. (Reference 38).

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13. ABSTRACT

A guide for conservative medical therapy for use in treating "surgical" illnesses encountered aboard Fleet Ballistic Missile (FBM) submarines is presented. Emphasis is placed on antibiotic drugs, their selection, administration, and contraindications. Newer concepts of 'massive' penicillin G therapy are detailed. Phases of supportive therapy adapted to shipboard facilities, include central venous pressure monitoring and a procedure for cross-matching blood. The epidemiology, detection, and treatment of penicillin allergic reactions are outlined. The paper concludes with practical suggestions concerning diagnostic tests and supply problems.

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