The Outcome of Staphylococcal Bacteremia in Childhood

"The Prognosis is Better Than Previously Reported"

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Fifty infants and children were treated for staphylococcal infections complicated by bacteremia. Of these, 28 had serious underlying diseases, principally leukemia (15 cases). All were treated with intravenous antibiotics for a median duration of 12.7 days. Although 13 patients died (26%), the staphylococcal infection had apparently been eradicated in all but three (6%), one of whom died before treatment could be started. The relatively brief treatment periods required in even severely compromised leukemic patients and the survival of all but one of 22 previously healthy patients with staphylococcal bacteremia suggest that the prognosis is better than previously reported.

BACTEREMIA during an infection with coagulase-positive staphylococci (CPS) has always been regarded as a serious development, and is still deemed life-threatening despite the advent of antimicrobial therapy. Although infants and children in recent studies have fared better than adults, mortality for patients under 20 has been reported to be between 25 and 50 per cent.[1–6]

This reported poor outcome of CPS bacteremia, the tendency for localized infections to spread, and the special gravity of staphylococcal endocarditis have led many clinicians to adopt the practice of treating all patients with CPS bacteremia with parenteral antibiotics for prolonged periods.[7,8]

Since CPS are a relatively frequent cause of bacteremia in infants and children,[9] questions of prognosis and optimal duration of treatment deserve attention. Seeking answers to these questions, we reviewed 50 cases of CPS infection with complicating bacteremia which were encountered during a recent three-year period at the Children's Hospital of Philadelphia.

Methods of Study

During the years 1971–1973, 76 patients at this hospital had blood cultures positive for CPS whose records could be traced. Of these, in 26 the cultures seemed to have been contaminated, and they received little or no treatment. The remaining 50 clearly had a serious staphylococcal infection and received treatment for it. Each child had one or more of the following attributes: a typical prostrating clinical illness and repeated isolation of staphylococci from the blood or strong evidence of a serious local infection.

From the Children's Hospital of Philadelphia, 34th and Civic Center Boulevard, Philadelphia, Pa. 19104.

TABLE 1. *Age Distribution of 50 Patients with Staphylococcal Bacteremia*

Age	Number
<1 month	5
1–6 months	7
6–12 months	4
1–4 years	13
4–10 years	13
>10 years	8

Information on the course of illness, timing and duration of antimicrobial therapy, and outcome were extracted from hospital records. Antibiotic sensitivity testing was performed by the standard Kirby-Bauer disk technique on all bacterial isolates. When tabulating duration of treatment, we considered only antibiotics to which the organism was proved sensitive.

Clinical and Bacteriologic Observations

Age and Sex. Patients ranged in age from one day to 15 years (Table 1). Sixteen were less than one year, and five were less than one month. More than half (29) were under four years of age, though children of all ages were affected. There were 34 boys, giving a sex ratio of 2.1:1.

Underlying diseases. Twenty-three patients had no serious underlying disease at the time of positive blood culture. Among the remaining 27 (Table 2), the most common disorder was leukemia (15 cases). Only one leukemic patient was in remission; the rest all had pancytopenia with neutrophil counts ranging from 0 to 880 per mm^3 (mean:170). Five other patients had hydrocephalus and infected ventricular shunts. None had underlying heart disease.

TABLE 2. *Underlying Disease at the Time of Positive Blood Culture*

Number	Disease
23	No underlying disease
13	Acute lymphocytic leukemia
2	Acute myelocytic leukemia
1	Biliary atresia
5	Hydrocephalus with shunts
1	Sickle cell disease
1	Panhypopituitarism
1	Thrombasthenia
1	Congenital adrenal hyperplasia
1	Gastroschisis
1	Insecticide poisoning

Antibiotic Sensitivities. Organisms isolated by blood cultures were uniformly susceptible to erythromycin, cephalothin, nafcillin, methicillin, lincomycin, and vancomycin. Ten were also susceptible to penicillin (20%). The proportion of penicillin-sensitive strains did not differ between hospital- and community-acquired infections.

Origin, Site and Spread of Staphylococcal Infection. Thirty-five of the 50 patients had 48 local sites of infection (Table 3). In the remaining 15, a local infection was not found. Symptoms in 10 of 51 infections (one patient was infected twice) developed during the hospital stay. Six patients had spread of their local infection to adjacent structures (*e.g.*, local abscess formation or empyema) at the time antimicrobial therapy was started.

Antimicrobial Treatment. All but two of the 50 patients were treated with antibiotics to which the organism was susceptible within three days of positive culture. Symptoms of infection preceded therapy by an average of 5.4 days. The intervals between onset of symptoms and initiation of treatment were similar in those with and those without evidence of spread to adjacent of distant sites (5.9 and 5.2 days, respectively). Five patients had had symptoms for ten or more days before receiving therapy.

Although initial therapy was variable, intravenous nafcillin was given eventually to all but six patients. Four of the latter were treated orally, and two were not treated. With 13 patients, an oral antibiotic was continued after a course of intravenous medication. The median duration of parenteral treatment for the series as a whole was 12.7 days. Table 4 shows duration of treatment for those successfully treated, grouped according to clinical phenomena. Treatment tended to be longest in patients with osteomyelitis and septic arthritis and shortest in those with soft-tissue infections. Length of treatment period was quite variable in leukemic patients (in whom a source of infection was found in only 5 of 14); the median was ten days. Patients with metastatic infection were treated on an average of about three days longer than the group as a whole.

Mortality. Thirteen patients (Table 5) died during their hospitalization and one more was discharged terminally ill. In only three of these did death seem directly due to the CPS infection (K.A., N.I., and A.A.). In the remainder, the CPS infection was a terminal event. Seven of these patients were leukemics in relapse and had neutropenia. One patient had an abscess at an intravenous injection site; after drainage, one of ten blood culture bottles again grew staphylococcus, but the patient died of *E. coli* sepsis and central nervous system (CNS) aspergillosis. In all the others, the blood cultures became uniformly negative for staphylococcus significantly before death. The longest interval between initiation of antimicrobial therapy and the first negative culture was 11 days.

Thus, although 13 died, death was attributed to staphylococcal infection in only three. All three were admitted gravely ill and died in the first week. The other fatal outcomes were the result of respiratory failure (1 case), gram-negative infection (8 cases), and glomerulonephritis (1 case). Of the ten patients who were autopsied, staphylococci were recovered from only two. Remarkably, none of the leukemic patients appears to have died of staphylococcal infection, and no patient developed infective endocarditis.

Discussion

CPS bacteremia was encountered in 50 patients at Children's Hospital of Philadelphia during the three years 1971–73. Although all age groups were affected, infants in the first year appeared particularly vulnerable.

Treatment was usually prompt and vigorous. Nevertheless, 11 patients had spread of infection by the time treatment was begun. Duration of therapy varied widely, being related to the source of infection and the clinical response in each case. Patients with leukemia were treated for a median duration of only 10 days. Of the patients successfully treated only 1 possible relapse occurred; this was in a child with leukemia and pancytopenia, in whom blood cultures again became positive 7 days after nafcillin therapy was stopped. Although tabulated as a re-infection, his second bacteremia may have been a relapse after inadequate treatment.

TABLE 3. *Sites of Involvement in 35 Patients in Whom Local Infection Was Found*

Sites of Involvement	Number
Skin and subcutaneous tissue	17
Bone	6
Shunt infection	5
Lung	5
Site of intravenous infusion	4
Deep soft tissue	3
Joint space	2
Cervical nodes	2
Pleural space	2
Operative site	1
Pericardium	1
Urinary tract	1
Intervertebral disk	1
Ascitic fluid	1
Conjunctiva	1

These observations suggest that the prognosis in CPS bacteremia in infancy and childhood is generally good with modern treatment. They certainly do not support the view that young patients should be treated for weeks. Even in severely compromised hosts, apparent eradication of the organism was usually achieved with a few days by antimicrobial therapy and drainage. Such hosts tended to succumb to infections caused by resistant gram-negative organisms.

It must be noted that none of our patients had underlying congenital or acquired

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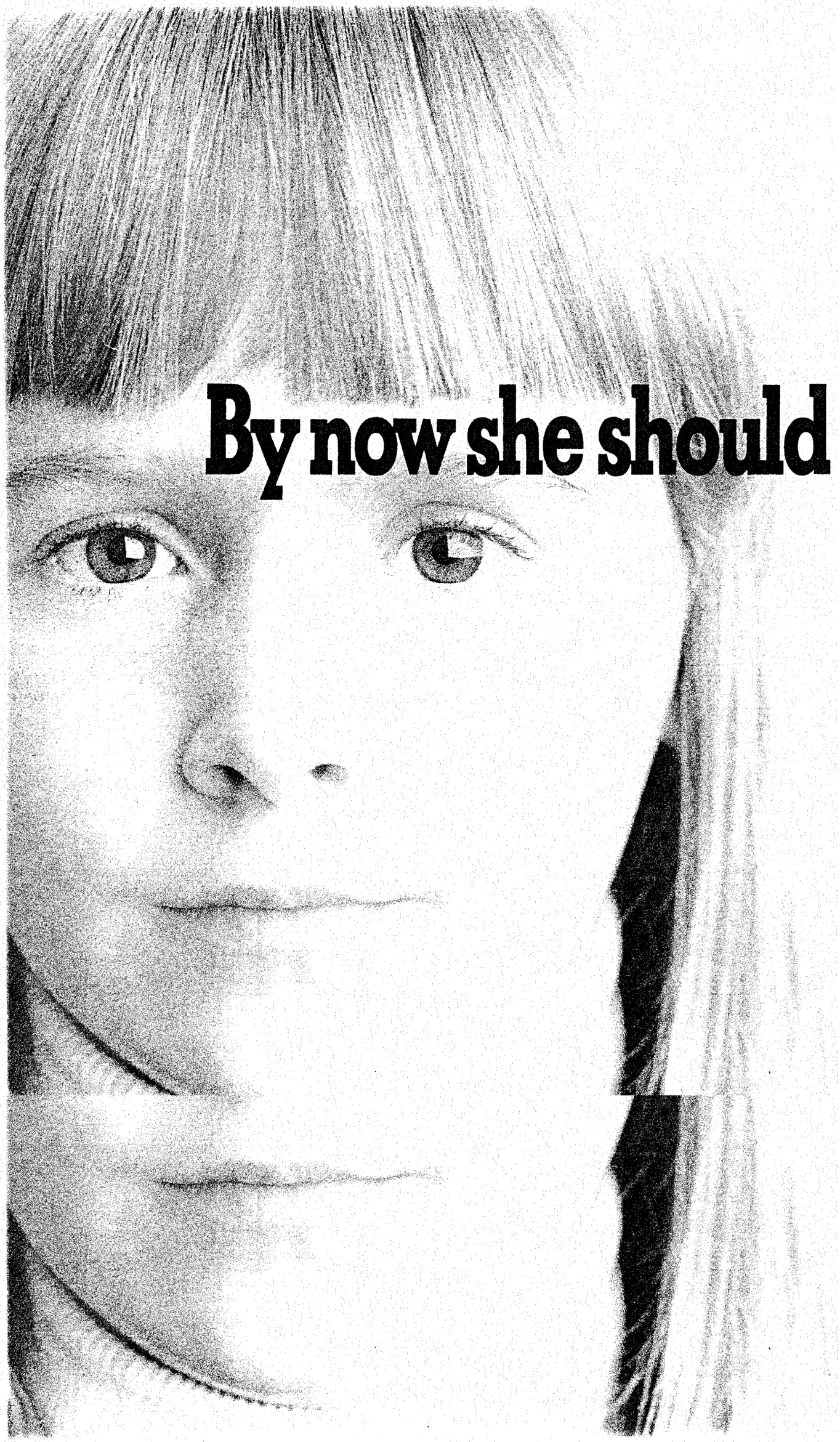
TABLE 4. *Number of Days of Antimicrobial Therapy for Individual Patients Successfully Treated*

Diagnosis	Days of Treatment	Median
All patients	—	12.7
No source found	3,3,6,6,7,8,9,9,10,10, 10,13,13,23	9
Osteomyelitis	14,20,20,21,21,41	20.5
Septic arthritis	19,20	19.5
Pneumonia	14,15,23	15
Soft tissue infection	5,6,6,6,7,11,12,14, 15,15	9
Shunt infection	10,11,13,20	12
Leukemic patients	3,3,6,6,6,9,10,10,11, 13,13,15,15,17,23	10
Spread of infection to more than one site	1,7,14,15,15,17,20,20, 23,41	16



Rheumatic fever prevention and the noncompliant patient.

Patients on oral penicillin for prevention of recurrent rheumatic fever usually don't ignore their daily dosage regimen deliberately. But since patients are only human, doses *are* missed occasionally—through simple lapse of memory, lack of time or insufficient drug on hand.

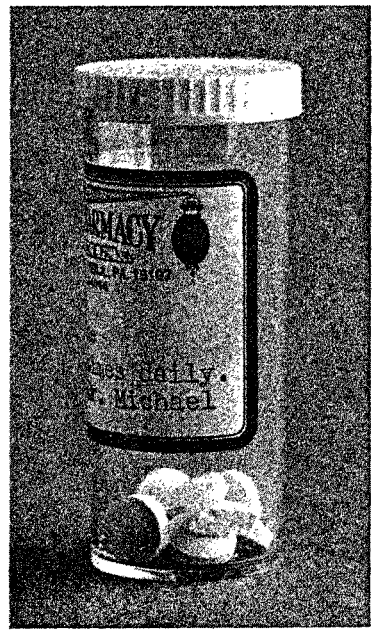
Prolonged penicillin blood levels to obviate need for daily dosage.

A single injection of benzathine penicillin G (1.2 million units) once a month provides continuous prophylaxis in most patients. Which is why it's recommended as the method of choice* to prevent streptococcal infection and possible recurrence of rheumatic fever.

A method of choice in treatment of strep pharyngitis, too.*

In therapy of mild to moderate Group A streptococcal pharyngitis without bacteremia, just one injection of 600,000 to 900,000 units usually maintains penicillin serum concentrations in children for the 10 days necessary to eradicate the infecting organisms.† In adults, 1.2 million units are required.

*Rheumatic Fever Committee of the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association.



have taken all of them.

FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Indications: In treatment of infections due to penicillin G-sensitive microorganisms susceptible to the low and very prolonged serum levels common to this dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and clinical response.

The following infections usually respond to adequate dosage of IM benzathine penicillin G.

Streptococcal infections (Group A—without bacteremia). Mild to moderate upper respiratory infections (e.g., pharyngitis).

Venereal infections—Syphilis, yaws, bejel, and pinta.

Medical Conditions in which Benzathine Penicillin G Therapy is indicated as Prophylaxis:

Rheumatic fever and/or chorea—Prophylaxis with benzathine penicillin G has proven effective in preventing recurrence of these conditions. It has also been used as followup prophylactic therapy for rheumatic heart disease and acute glomerulonephritis.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens. Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

†In streptococcal infections, therapy must be sufficient to eliminate the organism, otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of non-susceptible organisms including fungi. Take appropriate measures if superinfection occurs.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness-like reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high parenteral doses.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Composition: (units benzathine penicillin G as active ingredient in aqueous suspension):
300,000 units per cc.—10-cc. multi-dose vial. Each cc. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. povidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 1.2 mg. methylparaben and 0.14 mg. propylparaben.

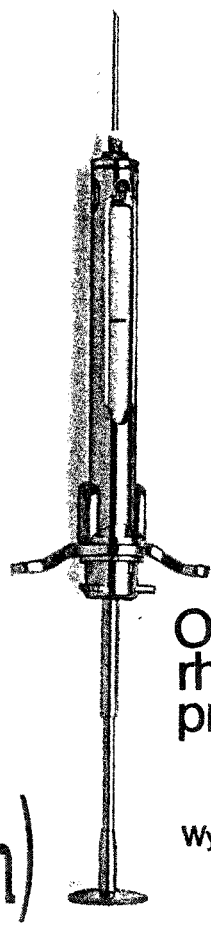
600,000 units in 1-cc. TUBEX® (sterile cartridge-needle unit) Wyeth, packages of 10.

900,000 units, 1.5-cc. fill in 2-cc. TUBEX, packages of 10.

1,200,000 units in 2-cc. TUBEX, packages of 10, and in 2-cc. single-dose disposable syringe, packages of 10.

2,400,000 units in 4-cc. single-dose disposable syringe, packages of 10.

Each TUBEX or disposable syringe also contains sodium citrate buffer and, as w/v, approximately 0.5% lecithin, 0.6% carboxymethylcellulose, 0.6% povidone, 0.1% methylparaben and 0.01% propylparaben.



INJECTION

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(sterile benzathine penicillin G suspension)

Once-a-month rheumatic fever prophylaxis.

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TABLE 5. *Findings in Thirteen Patients Who Died During Hospitalization*

Patient	Age	Underlying Condition	Site of Infection	Outcome	Autopsy Findings	Postmortem Culture
K.A.	3½ yrs	None	Lungs	Died of respiratory failure	Multiple lung abscesses	Blood—no growth Lung—staphylococcus Heart vegetation *K. pneumoniae*
N.I.	3 mon	Dandy-Walker malformation, hydrocephalus, ventricular shunt	Infected shunt, ventriculitis	Entered moribund, died next day	—	—
A.A.	2 yrs	Thrombasthenia	None found	Died shortly after arrival in hospital	Hemorrhages, hepatic necrosis	Staphylococcus coagulase positive in blood
R.C.	3 mon	Pneumonitis, unknown etiology, tracheostomy and ventilator therapy	I.V. site	Died of progressive respiratory failure	Report not available	Blood—alphahemolytic streptococcus; Lung—*Proteus mirabilis*
K.N.	2½ mon	Bronchopulmonary dysplasia	Lungs	Respiratory failure	Lung abscess, atelectasis, emphysema	Pseudomonas in lungs
C.T.	9 yrs	Insecticide poisoning	None found	Blood culture 4 days before death grew staph	Glomerulonephritis	Negative
J.C.	2 yrs	All in relapse	None found	Died with pancytopenia and fever	Multiple septic lesions lung, liver, kidneys; acute cerebral cortical hemorrhage	Spleen—*E. coli* Lung *E. coli*
L.E.	8½ yrs	All in relapse	None found	Died after 4 days antibiotics	Pulmonary hemorrhage, splenic abscess	Blood *E. coli* Lung *E. coli*
R.F.	4½ yrs	All in relapse	None found	Developed *E. coli* sepsis & massive gastrointestinal hemorrhage	Bronchopneumonia	Blood *E. coli* Lung *E. coli*
M.G.	11½ yrs	All in relapse	None found	Antibiotics stopped after 13 days; died with hectic fever 20 days later	Renal abscesses, pneumonia	Blood—*K. pneumoniae* Lung—*K. pneumoniae*
J.L.	6 yrs	All in relapse	IV site	Persistent fever despite negative culture; developed central nervous system leukemia & aspergillosis	Cerebral vasculitis, meningitis	Blood—*E. coli* Lung—*E. coli* Brain—alphahemolytic streptococci, *E. coli*
T.S.	8 yrs	All in relapse	None found	Continual hectic fevers; blood culture 3 days before death grew *E. coli*	—	—
K.D.	6½ yrs	All in relapse	None found	Died without antibiotic treatment; blood culture later positive for staph	Leukemia, sepsis	*E. coli* in blood

valvular heart disease. Bacteremia in patients with either of these conditions would have been treated for six weeks as bacterial endocarditis.

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