

STAPHYLOCOCCUS AUREUS MENINGITIS IN CHILDREN

A REVIEW OF 30 COMMUNITY-ACQUIRED CASES

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ABSTRACT - In spite of the steady increase in the incidence of *Staphylococcus aureus* infections, it remains a relatively uncommon cause of meningitis. To our knowledge, no series of community-acquired *S. aureus* meningitis (CASAM) restricted to children has been published. So far in this retrospective study we report our experience with CASAM in children, hospitalized from 1983 to 1998 at Nossa Senhora da Glória Children's Hospital (HINSG). During the sixteen-year study period, 2,319 new cases of acute pyogenic meningitis were diagnosed at HINSG. Community-acquired *S. aureus* was identified as the causative agent in 30 patients (1.3 percent). The predominantly spinal localization of the agent is stressed. In contrast with publications which analyze adults, it has a better prognosis.

KEY WORDS: meningitis, bacterial meningitis, staphylococcus meningitis, staphylococcus.

Meningite por *Staphylococcus aureus* na criança: revisão de 30 casos adquiridos na comunidade

RESUMO - Apesar da incidência das infecções por *Staphylococcus aureus* ter aumentado, este permanece como uma causa relativamente incomum de meningite. Até o presente momento, nenhum estudo sobre meningite comunitária causada por *S. aureus* (CASAM) restrito a infância foi publicado. Neste estudo retrospectivo nós relatamos nossa experiência com crianças internadas no período de 1983 a 1998 no Hospital Infantil Nossa Senhora da Glória (HINSG). Durante este período de 16 anos, 2.319 novos casos de meningites bacterianas agudas foram diagnosticados neste hospital. O *S. aureus* adquirido na comunidade foi identificado como agente etiológico em 30 pacientes (1,3%). Um provável tropismo deste agente pelas meninges espinhais foi enfatizado. Em contraste com publicações que analisaram adultos, a meningite comunitária por *S. aureus* em crianças teve um prognóstico melhor.

PALAVRAS-CHAVE: meningite, meningite bacteriana, meningite por estafilococo, estafilococo.

Staphylococcus aureus remains a versatile and dangerous pathogen in humans. The frequencies of both community-acquired and hospital-acquired staphylococcal infections have increased steadily, with little change in overall mortality^{1,2}. *Staphylococcus aureus* meningitis is an uncommon severe illness, that accounts for lethality rates ranging from 14 to 77 percent in various studies from the antibiotic era (Table 1). Although small series present frequencies of even 8.8 percent, large series register average frequencies of 1 percent, which is a more realistic percentage.

The first proved case of staphylococcal meningitis was described by Galippe in 1889, following suppuration of the lower jaw with multiple fistulous tracts, developed in a man aged 23 who had a large impacted wisdom tooth²¹. In 1892, Anthony reported the first "cryptogenic staphylococcal meningitis" in a robust soldier aged 23²¹. MacNeal, Frisbee and Blevins²² collected 48 cases of

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Table 1. Incidence and lethality rates of *S. aureus* meningitis in the literature.

Reference	Year	Bacterial meningitis	<i>S. aureus</i> meningitis		Lethality	
			Nº	%	Nº	%
Mulcare	1932-1942	329	5	1.5	5	100=
Mulcare ³	1949-1959	308	8	2.6	2	25
Carson ⁴	1944-1953	354	6	1.7	-	-*
Smith ⁵	1944-1953	409	6	1.5	2	33
Studdert ⁶	1949-1956	115	7	6.0	1	14
Hyland ⁷	1947-1956	160	14	8.8	7	50
Eigler ⁸	1948-1957	294	23	7.8	5	22
Quaade ⁹	1949-1959	658	10	1.5	6	60
Forbes ¹⁰	1955-1961	281	5	1.8	-	-*
Swartz ¹¹	1956-1962	207	13	6.3	10	77
Fraser ¹²	1935-1970	167	4	2.4	-	-*
Finland ¹³	1935-1972	572	42	7.3	27	64
Bastos ¹⁴	1958-1972	15,067	112	0.7	36	32
Bohr ¹⁵	1966-1976	875	19	2.2	4	21
Geiseler ¹⁶	1954-1976	1316	11	0.8	3	27
Roberts ¹⁷	1956-1981	710	21	3.0	3	14
Schlech ¹⁸	1978-1981	13,974	153	1.1	-	-*
Schlesinger ¹⁹	1976-1984	550	33	6.0	7	21
Lerche ²⁰	1966-1989	1,830	44	2.4	-	-*

= Before the antibiotic era. * Specific lethality could not be calculated with available data.

proved staphylococci meningitis from 1893 through 1941, and Teng and Meleney²³, in an review of the specialised literature, found forty additional cases from 1941 to 1948.

Prior to 1932 the only successes in treatment were reported from France, where it was proposed that many of the so-called primary infections were secondary to latent spinal infection. This type of case was called "la forme rachidienne primitive", and treated by laminectomy and drainage⁶. Staphylococcal bacteriophages (Schless, 1932) were given intrathecally with some benefit, and when sulphonamides (Roberts, 1941) were used as therapeutic agents, the situation began to brighten still further. But it was the introduction of penicillin by intrathecal and intramuscular injection, used in conjunction with sulphonamides (Evans, 1944), that first gave a prospect of cure in the majority of cases^{6,23}.

Recent studies have shown that within this disease entity there are considerable differences between the hospital-acquired and the community-acquired forms^{20,24}.

The hospital-acquired (nosocomial) form is the mildest and the most common of the two. It is primarily observed as an occasional complication to neurosurgical procedures, the presence of medical devices, or to certain skin infections. It is generally associated with a favorable prognosis and with a relatively low lethality rate.

In contrast, community-acquired *S. aureus* meningitis (CASAM), has mortality rates of 14-60 percent (Table 2), but only two investigations have previous dealt with the frequency of complications^{19,20}.

To our knowledge, no series of CASAM restricted to children has been published so far.

Table 2. Lethality from community-acquired *S. aureus* meningitis in the literature.

Reference	Year	Number of patients	Age	Lethality	
				N°	%
Studdert ⁶	1949-1956	7	18 m -47 y	1	14
Fong ²⁵	1966-1981	15	19 m -87 y	9	60
Lerche ²⁰	1966-1989	28	15 y -84 y	12	43
Jensen ²⁴	1986-1989	43	1 m -85 y	24	56
Gordon ²⁶	1976-1984	10	31 y -85 y	3	30
Present study	1983-1998	30	18 d -14 y	1	3.3
Total	—	138	18 d -87 y	51	37

d, days; m, months; y, years.

METHOD

Records for the sixteen-year period between January 1, 1983 and December 31, 1998 were reviewed.

For the diagnosis, all of the following criteria were met: 1) clinical presentation compatible with meningitis (e.g., fever, headache, and meningeal irritation signs); 2) cerebrospinal fluid (CSF) leukocyte count ≥ 100 cells/mm³ with > 50 percent neutrophils, and 3) positive CSF culture for *S. aureus*. In cases with a negative CSF culture, a positive blood culture with *S. aureus* associated with a CSF leukocyte count ≥ 100 cells/mm³ with > 50 percent neutrophils was considered indicative of *S. aureus* as the etiologic agent. Patients with a positive blood culture for *S. aureus* with CSF leukocyte count < 100 cells/mm³ and a negative CSF culture were not included. Such patients were presumed to have meningeal irritation without meningitis.

Patients who suffered craniospinal axis trauma or who presented visible malformation, like meningomyelocele, were not included.

A community-acquired infection is defined as being present of incubating at the time of admission, and not related to present or previous hospitalization, according with guidelines provided by the Center for Diseases Control (CDC) - USA.

Medical data from each patient were recorded on standardized charts. The data included information on patient identification (e.g., gender and age), clinical history, predisposing conditions, possible foci of infection, physical findings, laboratory findings, antibiotic treatment, complications, sequelae on discharge and lethality.

The initial treatment (i.e., that given until the bacteriologic diagnosis and the resistance pattern of the infecting strain were determined) was penicillin associated with chloramphenicol. After the diagnosis of CASAM, all the 30 patients were treated with penicillinase-resistant penicillin (oxacillin), alone or associated with other antibiotics (rifampicin, aminoglycoside or both). The association between two or three antibiotics was based on the severity of the clinical picture. The minimal treatment duration was 3 weeks.

RESULTS

During the time period studied, 2,319 new cases of acute pyogenic meningitis were diagnosed at HINSG. Community-acquired *S. aureus* meningitis was identified as the causative agent in 1.3 percent of patients. The male-female ratio was 2.75 (22 males : 8 females). Table 3 shows details of age and gender distribution.

Foci and predisposing conditions

A probable focus for the hematogenous spreading to the meninges was found in 80 percent of the patients. Skin infections were found in 9 patients (30 percent). Periorbital cellulitis was found in 7 patients (23.3 percent), pneumonia in 5 (16.6 percent), acute otitis media in 3 (10 percent), arthritis in 2 (6,6 percent) and sinusitis in 1 patient (3,3 percent). No focus was found in the remaining 6 patients (20 percent). Two possible foci of entrance were found in 3 patients, so the total number of foci exceed the total number of patients.

Table 3. Age and gender distribution in 30 patients with *S. aureus meningitis*.

Age	Male		Female		Total	
	n°	%	n°	%	n°	%
0 – 28 days	0	0	1	3.3	1	3.3
29 days – 23 months	1	3.3	1	3.3	2	6.6
2 – 5 years	8	26.6	1	3.3	9	30
6 – 9 years	6	20	4	13.3	10	33.3
10 – 14 years	7	23.3	1	3.3	8	26.6
Total	22	73.2	8	26.5	30	100

Predisposing conditions (e.g., diabetes mellitus, immunodeficiency, alcohol/drugs abuse, cancer and occult abnormalities allowing for communication between the central nervous system (CNS) and a normally nonsterile environment) were not found.

Clinical findings

At admission all patients presented fever and 82.8 percent had nuchal rigidity. More than one third of the patients presented abdominal pain, that was as frequently as vomiting and more frequently than headache. The clinical features are shown in Table 4. Many patients, mainly those in school age, presented a remarkable column rigidity associated with nuchal rigidity with preservation of the conscience level. These patients were not capable to sit on the bed and when they could do it, they did presented in the tripod position of Amós, like the patients with poliomyelitis on the pre-paralytic phase or only with the meningeal form. These alterations many times had a parallelism with the finding of an intense hiperproteinorrhachia that created difficulty in liquor drainage, showing that the picture was of a predominantly spinal, rather than cerebral irritation and persisted for many days. Fever, generalized muscular pains and vomiting were commonly present, but the general condition was remarkably good for such an obviously severe infection. Some patients presented delirium, that is a common presentation in infectious diseases. However, its prolonged duration was remarkable in these patients, taking days to disappear.

Table 4. Symptoms and signs at presentation in 27 patients* with *S. aureus meningitis*.

Symptoms and signs	N°	%
Fever	27	100
Nuchal rigidity	25	92.6
Brudzinski sign	21	77.8
Kernig sign	14	51.8
Abdominal pain	13	48.1
Vomiting	12	44.4
Headache	11	40.7
Constipation	9	33.3
Lumbar pain	8	29.6
Irritability	5	18.5
Sleepiness	4	14.8
Delirium	3	11.1
Diarrhea	2	7.4
Torpor	2	7.4

*Only patients older than 2 years.

Table 5. Findings in cerebrospinal fluid (CSF) or blood samples of patients with *S. aureus* meningitis at presentation.

	Nº	%
Unclear CFS	23	76.6
CSF white cell count		
< 100/mm ³	2	6.6
100/mm ³ - 1000/mm ³	12	40
> 1000/mm ³	16	53.3
> 50% neutrophils	30	100
CSF glucose < 50 mg/dl or 50% of serum level	14	46.6
CSF protein		
< 40 mg/dl	6	20
40 mg/dl - 200 mg/dl	17	56.6
> 200 mg/dl	6	20
CSF Gram stain positive	6	20
CSF culture positive	15	50
White blood cell count		
> 10,000	22	73.3
≥ 80% neutrophils	24	80
Blood culture positive	21	70

Laboratory findings

Cerebrospinal fluid. CSF samples were obtained in all 30 patients and findings are given in Table 5. Two patients presented the CSF leukocyte count < 100 cells/mm³ in the first exam, but both had latterly confirmed the meningitis with positive CSF cultures for *S. aureus* and, in the subsequent exams both presented the CSF leukocyte count > 100 cells/mm³. In 20 percent of the cases, Gram positive cocci were found by microscopy. Positive CSF cultures for *S. aureus* were obtained in 50 percent of the patients.

Blood culture. Samples were obtained in all 30 patients. Positive blood cultures for *S. aureus* were obtained in 70 percent of the patients.

Antibiogram. Penicillin G was tested in 19 patients and all showed resistance to it. On the other hand, all the 21 patients tested to oxacillin, the 19 patients tested to vancomycin and the 13 patients tested to rifampicin were sensible to it. Rifampicin and trimethoprim-sulfamethoxazole were tested in 16 patients; 2 of them were resistant and the remaining ones were sensible.

Treatment and outcome

The treatment used after the diagnosis of CASAM was oxacillin alone by 6 patients. Oxacillin with aminoglycoside and oxacillin with rifampin were used by 8 and 12 patients, respectively. Four children were treated with the association oxacillin, aminoglycoside and rifampin. Vancomycin was not used.

Ten patients (33.3 percent) presented motor sequelae on discharge. Only one patient died. Some patients presented more than one type of motor sequel, like the association between hemiparesis and ophthalmoplegia.

DISCUSSION

Although several series have appeared over the past 40 years, *S. aureus* meningitis has received less attention in the specialised literature than its clinical importance warrants and very few investigations on community-acquired *S. aureus* meningitis (CASAM) have been reported. In our study, there were 30 cases of CASAM in 2,319 patients with bacterial meningitis during the period from 1983 to 1998, corresponding to a frequency of 1.3 percent. This is in accordance with the unique study that we found in the literature which compares the number of patients with CASAM and the total number of patients with bacterial meningitis²⁰.

The *S. aureus* meningitis following neurosurgery or craniospinal trauma can arise by two pathogenetic mechanisms: colonization of the wound or shunt with local extension to the CSF or hematogenous spread²⁷. The former mechanism is more likely to occur and is related to the colonization of skin and mucous membranes with the organism and to the ability of *S. aureus* to evade host defense systems in the presence of a foreign body. It forms a nidus of infection from which the organisms spread by local extension or dissemination. *S. aureus* adheres to the artificial surface by binding fibronectin, fibrinogen or laminin. The presence of the foreign body significantly interferes with host defense; the subcutaneous dose of *S. aureus* necessary to cause a soft tissue infection is dramatically decreased by the introduction of a suture. This effect appears to be mediated, in experimental systems, by a decreased capacity of host phagocytes to kill *S. aureus* in the setting of a foreign body²⁷.

The pathogenesis of *S. aureus* meningitis in patients without prior CNS disease is most often related to hematogenous dissemination, although *S. aureus* meningitis sometimes arises from local extension to the subarachnoid space²⁷. Bacteremia is detected more frequently in patients with spontaneous meningitis, that is, meningitis not associated with CNS surgery or trauma. Positive blood culture was found in 70 percent of our patients.

In contrast with the high incidences of predisposing conditions (e.g., diabetes mellitus, alcohol/drugs abuse, immunodeficiency and cancer), varying from 50 to 100 percent in publications that analyze mainly adults with CASAM^{20,24-26}, in our study that analyzes CASAM only in children predisposing conditions were not found.

A probable focus for the hematogenous spreading to the meninges of *S. aureus* was found in 80 percent of the patients. This is in accordance with previous reports, that varies from 44 to 100 percent^{6,20,24-26}.

Dermal sinus tracts may occur anywhere along the craniospinal axis. Though not all dermal sinus tracts enter the CNS, some will allow communication between the nonsterile skin environment and the CNS. Bacteria that usually inhabit the skin may then cause meningitis. Other investigators have noted that a careful search for a dermal sinus tract should be undertaken for any patient with staphylococcal meningitis²⁸.

Occult CNS abnormality allowing for communication between the CNS and a normally nonsterile environment were not found.

The frequency of fever and nuchal rigidity in the present study is in accordance with previous reports^{20,24-26}.

The presence of remarkable irritation meningeal signs and abdominal pain associated with the conscience level preservation was found in 40 percent of our patients with more than 2 years. These findings associated with a probable focus of infection is highly suggestive of staphylococcal etiology.

In 1929, Chavani & George²⁹ said: "these bacteria do not seem to have affinity to develop infections in meningeal spaces". Probably there is a repugnancy of *S. aureus* for the meninges. They described a form that they called "la forme rachidienne primitive" divided in an acute and a subacute type, that has been caused by a focus of infection on the vertebral column (e.g., osteitis). They thought that it was a very special form that deserves individualization.

In 1958, Studdert⁶ emphasized that an overwhelming complaint in each case was of backache rather than headache and that a striking feature was the absence of mental clouding, disorientation, and convulsions. The picture was that of a predominantly spinal, rather than cerebral, irritation. Fever, generalized muscular pains, vomiting, and restlessness were commonly present, but the general condition was remarkably good for such an obviously severe infection. In a patient autopsy, the meningeal changes were marked in the spinal canal, but much less obvious at the base of the brain, and virtually absent over the vertex. Owing to these findings, he thought that the predominantly spinal localization of the meningitis in this series makes the theory that that form of meningitis is secondary to epidural suppuration attractive. These findings were also observed by Mühler and Andres³⁰.

We have two reasons for citing the descriptions of these authors in detail; first, because this intense meningeal involvement with few conscience compromising also were found in many of our patients and we consider it very suggestive of staphylococcal etiology. Second, because it is remarkable that a fact like this was practically ignored in all the most recently literature consulted.

Due to the few number of meningitis caused by *S. aureus* comparing with the large number of other staphylococcal infections, it is noted that *Staphylococcus* does not have affinity for meninges. But when meningitis occurs, although there are not proves about it, it is reasonable to think about a tropism of *S. aureus* for the spinal meninges producing a clinical picture composed by remarkable paravertebral muscle rigidity and abdominal pain, both caused by an irritate process of spinal nerves and preservation of the conscience level.

Laboratory findings have not revealed a specific pattern for *S. aureus* meningitis, which in common to other bacterial meningitis. The majority of patients in our series had elevated CSF protein levels and leukocytes, though the CSF may be normal early in the infection. Gram stains had a low rate of positive results (28.6 percent); this result is in agreement with two recently reported studies, in which gram stains were positive in only 25 and 32 percent of cases, respectively^{19,25}.

CNS sequelae were significant in our patient population, but its analysis was incomplete because longer-term follow-up was not recorded.

Our clinical retrospective analysis did not permit us to make definite suggestions regarding optimal antibiotic therapy.

Penicillin G remains the drug of choice if the isolated *S. aureus* is sensitive to it¹. In these cases, oxacillin would be only one fourth to one hundredth as effective as penicillin G³¹.

A semi-synthetic penicillin (nafcillin or oxacillin) is indicated for β -lactamase producing strains which are susceptible to them^{1,19}. Nafcillin and oxacillin are four times more potent than methicillin against *S. aureus*³¹. Studies have indicated that the minimal inhibitory concentrations (MIC) of nafcillin for susceptible *S. aureus* range from 0,08 to 1,25 $\mu\text{g/ml}$, with averages of 0,312 to 0,6 $\mu\text{g/ml}$ ³². Nafcillin enter the CSF reasonably well in patients with severe meningeal inflammation, although great variability exists¹⁹. Clinical trials suggest that nafcillin concentration in the CSF during meningitis usually exceeds the minimum bactericidal concentrations (MBC) for *S. aureus* at least 3-fold¹⁹. The recommended dose is 200 mg/kg/day until 12 to 18 g/day¹⁹. We used oxacillin in 6 patients; 3 patients presented sequelae on discharge and no death occurred in this group.

Chloramphenicol exhibits some activity against *S. aureus* isolates that are methicillin-susceptible; yet, despite the excellent CNS penetration of this antibiotic, the results of therapy have been disappointing³³.

A major problem in therapy of staphylococcal infections in CNS and elsewhere occurs when the isolate is resistant to the semi-synthetic penicillins. In the United States about 50 percent of coagulase-negative staphylococci and 10 percent of coagulase-positive staphylococci are methicillin-resistant³³.

Vancomycin is the drug of choice for methicillin-resistant isolates or patients allergic to penicillin (those with a history of anaphylactic reactions)¹. Since its introduction into clinical practice, vancomycin

has been the subject of intensive investigation. The data available are based on inconsistent methodologies and small sample sizes, making it difficult to formulate conclusions about effectiveness. It is evident that vancomycin CSF concentrations adequate for bacterial eradication can be achieved in a variety of settings. It is also evident that given the narrow therapeutic profile of vancomycin, such concentrations cannot be consistently assured³⁴. No comparative randomized studies of vancomycin vs. nafcillin or oxacillin establish the superior drug in human disease¹⁹.

Teicoplanin, a new glycopeptide, has shown excellent *in vitro* activity against Gram-positive bacteria, including *Staphylococcus* sp³³. It has the same activity against *S. aureus* but it is less active against *S. epidermidis* than vancomycin, however it penetrates poorly into CSF³³. In experimental meningitis of rabbits, an infusion of mannitol increase of teicoplanin levels in the CSF³⁵.

The greatest interest has been shown in trimethoprim-sulfamethoxazole, owing to its high penetration into CSF and its frequent activity against both methicillin-susceptible and methicillin-resistant staphylococci^{33,36}. This form of therapy should be reserved for clearly documented refractory cases¹⁹. We used it orally to complete the treatment in patients that presented a good evolution.

The excellent diffusion of pefloxacin into cerebrospinal fluid of patients with meningitis is an alternative for older children³⁷.

Antimicrobial combinations have been used to increase bactericidal activity or to prevent the development of antimicrobial resistance. The combination of β -lactams and aminoglycosides increases bacterial killing *in vitro* and in animal models of endocarditis^{1,37}.

Rifampin is another potent anti-staphylococcal drug, which penetrates well into the CSF, but resistance invariably develops if it is used alone. One unique characteristic of rifampin that makes it useful as an anti-staphylococcal agent is its ability to penetrate leukocytes and kill intracellular organisms²⁶.

Although *in vitro* studies show conflicting results with regards to antagonism versus synergism, when rifampin is used with vancomycin it appears to be method-dependent^{19,38}. The previous finding of synergism between vancomycin and rifampin by the checkerboard method may not be true synergism but merely suppression of rifampin resistance by vancomycin³⁸.

Several case reports have shown improved clinical outcome in the treatment of serious staphylococcal infections when rifampin was added to other antibiotics - penicillinase-resistant penicillins, cephalosporins, vancomycin, and aminoglycosides^{26,39}. This antibiotic has excellent bactericidal activity against both methicillin-susceptible and methicillin-resistant organisms, penetrate well into the CSF, and has the additional benefit of intraleukocytic killing of the organism. Combination therapy with vancomycin or nafcillin also appears to prevent the emergence of rifampicin resistance^{19,37}. We used a combination of rifampin, oxacillin and aminoglycoside in 4 patients and other combination of oxacillin and rifampin in 12 patients, occurring fewer number of sequelae using the first combination. Although our clinical retrospective analysis did not permit us to make definite suggestions regarding optimal antibiotic therapy, we believe that the better choice is oxacillin plus rifampin.

In conclusion, community-acquired *S. aureus* meningitis in children was a relatively uncommon but serious cause of meningitis in our patients population but in contrast with publications which analyze adults, community-acquired *S. aureus* meningitis in children has a better prognosis. Suggestion for optimal antibiotic therapy and duration of therapy continue to rest on the retrospective clinical studies, case reports, and animal models.

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