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Authors

Heizer, Heather
Gaensbauer, James
Dodson, Daniel

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MAJOR ARTICLE

Sequential Intravenous-Oral Therapy for Pediatric *Streptococcus anginosus* Intracranial Infections

Daniel S. Dodson,[1,2] Heather R. Heizer,[2] and James T. Gaensbauer[2,3]

[1]Section of Pediatric Infectious Diseases, Department of Pediatrics, University of California, Davis, Sacramento, California, USA, [2]Section of Infectious Diseases, Department of Pediatrics, University of Colorado School of Medicine, Aurora, Colorado, USA, and [3]Division of Pediatric Infectious Diseases, Department of Pediatrics and Adolescent Medicine, Mayo Clinic, Rochester, Minnesota, USA

Background. *Streptococcus anginosus* group is a common cause of pediatric intracranial infections but treatment recommendations, including use of oral therapy, are poorly defined.

Methods. We performed a retrospective review from 2004 to 2019 of all patients with *S anginosus* group pyogenic intracranial infections at Children's Hospital Colorado, highlighting patients transitioned to oral therapy. The primary endpoint was worsening infection necessitating intravenous antibiotics or a source control procedure after transition to oral therapy.

Results. Of 107 patients with *S anginosus* intracranial infections, 61 were transitioned to exclusive oral therapy after a median intravenous duration of 37 days, overwhelmingly with a levofloxacin-based regimen. Only 1 treatment failure was noted in a patient who did not fill their prescription. Patients with epidural infections were more likely to be transitioned to oral therapy within the first 28 days of treatment (defined as "early"). Patients with parenchymal infections, bacteremia, co-pathogens, higher inflammatory markers, and requiring >1 source control procedure were less likely to be transitioned early to oral therapy. Complications of a central catheter and/or intravenous medications contributed to 56% of oral transitions.

Conclusions. Levofloxacin-based oral regimens were effective and well tolerated. Patients with less severe infections were more likely to be transitioned early to oral therapy. Criteria for transitioning patients to oral antibiotics for intracranial infections should be established to minimize risks inherent with central catheters.

Keywords. intracranial infection; levofloxacin; oral therapy; *Streptococcus anginosus*.

Pediatric intracranial pyogenic infections are an uncommon but morbid condition [1–3]. Among such infections, *Streptococcus anginosus* group is the most frequently identified organism in several case series with contiguous sources such as sinusitis and mastoiditis frequent predisposing conditions [4–9]. Treatment recommendations for these infections vary considerably and no pediatric guidelines exist. Suggested length of antimicrobial therapy varies from 2 weeks to beyond 3 months, with 4–8 weeks being most common and recommended by the Working Party in the United Kingdom in 2000 [2, 7, 8, 10–16]. Effectiveness and timing of oral therapy are debated, though patients have been successfully transitioned to oral antibiotics at 1–2 weeks of therapy [1, 17–21].

Oral therapy eliminates the risks of a central catheter including bloodstream infection, venous thrombosis, and catheter malfunction, and is now routine for conditions previously treated with prolonged intravenous (IV) therapy such as pediatric osteomyelitis [22]. Given the advantages of oral therapy, we sought to identify patients with *S anginosus* group purulent intracranial infections and analyze characteristics and outcomes of patients transitioned to oral therapy.

METHODS

Study Population

We performed a retrospective review of pyogenic intracranial infections caused by *S anginosus* group at Children's Hospital Colorado from January 2004 through February 2019 for patients 21 years of age or younger. A list of all positive cultures for *S anginosus* group from any source was obtained from an electronic medical record–based database. Medical records of these patients were individually reviewed for inclusion. Inclusion criteria were radiologic evidence of an infected intracranial parenchymal, subdural, or epidural fluid collection AND a positive culture for *S anginosus* group from an intracranial source, specific extracranial sources (sinus, scalp abscess, orbit), or from blood. Patients with "dural enhancement" or similar radiologic findings not clearly a fluid collection were excluded. Our laboratory identifies *S anginosus* to the group level, so species data were not available.

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Correspondence: Daniel S. Dodson, MS, MD, Section of Pediatric Infectious Diseases, Department of Pediatrics, University of California, Davis, 2516 Stockton Blvd, Sacramento, CA 95817, USA (dsdodson@ucdavis.edu).

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Data Collection and Definitions

We reviewed inpatient clinical course, outpatient infectious disease clinic notes, and other available encounters for demographic, clinical, radiologic, laboratory, and outcomes data. All outpatients were followed in the infectious disease clinic unless lost to follow-up. Location of intracranial infection, presumed primary source of infection, and infectious complications were determined from radiology reports and medical documentation. Co-pathogens were defined as additional organisms found in cultures except coagulase-negative *Staphylococcus* spp from blood, which was considered a contaminant. Beginning of therapy was defined as the date of the last intracranial source control procedure or, if no source control procedure was done, the beginning of directed antibiotic therapy. Sinus aspiration, orbital abscess drainage, and other extracranial procedures were not considered intracranial source control procedures. Date of oral transition was defined as the first day the patient was treated exclusively with oral antibiotics. Data were stored using the REDCap electronic database [23].

Endpoints and Analysis

The primary endpoint was failure of oral therapy, defined as worsening infection while on oral antibiotics requiring reinitiating IV therapy or a source control procedure. Additional endpoints were timing of transition to oral therapy and reason for transition to oral therapy. Transition to exclusive oral therapy was defined as "early" if done at <28 days from the beginning of therapy and "late" if done at ≥28 days. Comparisons of endpoints with categorical variables were done using Fisher exact test. Comparisons using continuous variables were done using Wilcox-Mann-Whitney test. Significance was defined as $P < .05$. Statistical analysis was done using Stata software version 16. Patients with missing data were excluded from analysis using the missing variable (eg, patients without a repeat C-reactive protein [CRP] prior to starting oral therapy were not included in calculating median CRP prior to oral therapy). The lowest CRP reported by our laboratory is <5 mg/L. Values <5 mg/L were treated as 5 mg/L for statistical analysis.

This study was approved by the Colorado Multiple Institutional Review Board and was deemed exempt due to retrospective nature.

RESULTS

Patient Population

We identified 1221 unique patients with any positive culture for *S anginosus* group. Of these, 107 met inclusion criteria, 45 completed treatment with IV therapy, 61 were transitioned to exclusive oral therapy, and 1 patient was lost to follow-up immediately after hospital discharge (excluded from comparative analyses as oral transition is unknown). One patient, a 3-year-old with a subdural abscess treated intravenously, died due to complications of a massive stroke within 1 week of diagnosis. The

Table 1. Patient Demographics and Infection Characteristics (N = 107)

Characteristic	No. (%)
Overall	107 (100)
Age, y, median (IQR)	11.5 (8.1–13.8)
Female sex	37 (35)
Race	
American Indian or Alaskan Native	1 (1)
Asian	6 (6)
Black or African American	9 (8)
White	76 (71)
Other	12 (11)
Not stated	3 (3)
Ethnicity	
Hispanic or Latino	19 (18)
Not Hispanic or Latino	84 (79)
Other	1 (1)
Not stated	3 (3)
Location of infection	
Epidural collection	61 (57)
Subdural collection	42 (39)
Parenchymal collection	33 (31)
Mutually exclusive intracranial diagnoses	
Epidural collection only	42 (39)
Subdural collection only	20 (19)
Parenchymal collection only	20 (19)
Epidural and subdural collection	12 (11)
Epidural and parenchymal collection	3 (3)
Subdural and parenchymal collection	6 (6)
Epidural, subdural, and parenchymal collection	4 (4)
Presumed source of infection	
Sinus	78 (73)
Otogenic	8 (7)
Trauma	3 (3)
Hematogenous or unknown	18 (17)
Infectious complications	
Dural venous sinus thrombosis	14 (13)
Cavernous venous sinus thrombosis	5 (5)
Orbital abscess	16 (15)
Osteomyelitis	31 (29)
Bacteremia	14 (13)
Coinfections	
Any coinfection	64 (60)
Any coinfections except CoNS	52 (49)
MSSA	15 (14)
MRSA	2 (2)
CoNS	27 (25)
Other *Streptococcus* spp	12 (11)
Other gram-positive aerobes	5 (5)
Gram-negative aerobes	15 (14)
Gram-positive anaerobes	12 (11)
Gram-negative anaerobes	10 (9)
Year diagnosed	
2011 or before	34 (32)
2012–2015	37 (35)
2016 or after	36 (34)
Source control procedures	
Any	64 (60)
>1	16 (15)

Abbreviations: CoNS, coagulase-negative staphylococci; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

median patient age was 11.5 years and 35% of patients were female (Table 1). Differences in treatment based on demographics were not statistically significant. Of the 61 patients transitioned to oral antibiotics, 7 (11%) were transitioned at <14 days from initiation of therapy, 13 (21%) between 14 and 27 days, 15 (25%) between 28 and 41 days, and 26 (43%) at ≥42 days.

Outcomes

Of the 61 patients treated with oral therapy, 1 patient met criteria for failure. This patient had an epidural abscess with source control and was initially treated with ceftriaxone, metronidazole, and vancomycin. They were prescribed oral levofloxacin and metronidazole at ≥42 days of therapy but did not fill their prescription and subsequently developed worsening infection necessitating restarting IV antibiotics and a source control procedure. A second patient restarted IV ceftriaxone after a presumed drug reaction to oral levofloxacin but did not have worsening infection. No other patient needed to restart IV antibiotics after oral transition, though 5 patients were lost to follow-up after oral transition (4 patients transitioned early vs 1 patient transitioned late; $P = .04$) prior to completion of therapy. Of note, 1 patient treated exclusively with IV therapy needed to restart antibiotics 4 months after therapy completion due a bone flap infection but did not have recrudescence of intracranial infection. No other patients are known to have restarted antibiotics after therapy completion.

The median total duration of therapy was 59 days (73 days for those treated orally vs 50 days for those treated exclusively IV; $P < .001$). Those transitioned early to oral therapy had a median total duration of 48 days (33 days orally) compared to 83 days (35 days orally) for those transitioned later ($P < .001$ for total duration, not significant for oral duration).

Diagnoses

Of the 107 overall patients, an epidural fluid collection (61 patients [57%]) was the most common intracranial diagnosis, followed by subdural and parenchymal infections (39% and 31%, respectively) (Table 1). Though transition to oral therapy was not statistically different between those with epidural, subdural, and parenchymal fluid collections, patients with epidural collections were more likely to be treated with early oral therapy ($P < .001$) and patients with parenchymal infections were less likely to treated with early oral therapy ($P = .006$) (Table 2). Most infections were attributed to complicated sinusitis (78 patients [73%]). Infectious complications included dural venous sinus thrombosis (14 patients [13%]), cavernous venous sinus thrombosis (5 patients [5%]), orbital abscesses (16 patients [15%]), osteomyelitis (31 patients [29%]), and bacteremia (14 patients [13%]) (Table 1). Patients with bacteremia were less likely to be treated with early oral therapy ($P = .04$) (Table 2). Otherwise, differences in treatment course by complication were not significant, though sample sizes were low.

Microbiology

Of the 107 overall patients, the most common co-pathogen was coagulase-negative *Staphylococcus* species (27 patients [25%]). Other organisms included methicillin-susceptible *Staphylococcus aureus* (MSSA) (15 patients [14%]), gram-negative aerobes (15 patients [14%]), other *Streptococcus* spp (12 patients [11%]), and gram-positive anaerobes (12 patients [11%]) (Table 1). Two patients (2%) had methicillin-resistant *S aureus* (MRSA) and were treated entirely with IV therapy. No *Streptococcus pyogenes* was found. Patients with a co-pathogen were less likely to transition to early oral therapy ($P = .03$). This difference did not remain significant if coagulase-negative *Staphylococcus* was excluded (Table 2).

Our *S anginosus* group isolates were 96% susceptible to penicillin (76 isolates tested), 99% susceptible to ceftriaxone (72 isolates tested), 100% susceptible to vancomycin (75 isolates tested), and 100% susceptible to levofloxacin (25 isolates tested). Levofloxacin susceptibility was not associated with transition to oral therapy.

Laboratory and Imaging Data

Peak CRP and erythrocyte sedimentation rate (ESR) values, and values prior to oral transition (obtained at a median of 30 days of therapy), are shown in Table 3. The median peak CRP was 110 mg/L and decreased to <5 mg/L in those transitioned to oral therapy. Of the 58 patients transitioned to oral therapy with a CRP value prior to transition, 51 (88%) had a CRP ≤10 mg/L at the time of oral transition. The median peak ESR was 67 mm/hour and decreased to 12 mm/hour in those transitioned to oral therapy. Of the 57 patients transitioned to oral therapy with an ESR obtained prior to transition, 41 (68%) had an ESR ≤20 mm/hour at the time of transition. No difference in peak CRP or ESR was seen when comparing those transitioned to oral therapy to those treated with exclusive IV therapy. However, patients transitioned to early oral therapy had a lower peak CRP (61 mg/L vs 157 mg/L; $P = .01$) and ESR (38 mm/hour vs 77 mm/hour; $P = .04$) than those transitioned later. Conversely, patients transitioned early to oral therapy had higher CRP and ESR at the time of oral transition than those transitioned later.

Of the 61 patients transitioned to oral therapy, 44 (72%) had repeat imaging prior to transition (excluding immediate postoperative imaging). Of these 44 patients, 12 (27%) had resolution or near resolution of intracranial purulence, 29 (66%) had improvement, 2 (5%) were stable, and 1 (2%) appeared worse. Repeat imaging done about 1 week after oral transition showed interval improvement in this patient with worsening imaging.

Initial Therapy

The most used IV antibiotics in the 107 overall patients were ceftriaxone (102 patients [95%]), metronidazole (102 patients [95%]), and vancomycin (103 patients [96%]). At least 1 intracranial source control procedure was performed in 64 patients (62%).

Table 2. Patient Characteristics Stratified by Treatment Course (n = 106)

Characteristic (No.)	Treatment Group: Transitioned to Oral <28 Days (n = 20) No. (Row %)	Transitioned to Oral ≥28 Days (n = 41) No. (Row %)	*P* Value (<28 vs ≥28 Days)	All IV Therapy (n = 45) No. (Row %)	*P* Value (Any Oral vs IV)
Location of infection					
Epidural collection (61)	19 (31)	20 (33)	**< .001**	22 (36)	.16
Subdural collection (42)	4 (10)	19 (45)	.06	19 (45)	.69
Parenchymal collection (32)	1 (3)	16 (50)	**.006**	15 (47)	.67
Mutually exclusive intracranial diagnoses					
Epidural collection only (42)	15 (36)	13 (31)	**.002**	14 (33)	.16
Subdural collection only (20)	1 (5)	7 (35)	.25	12 (60)	.09
Parenchymal collection only (19)	0 (0)	9 (47)	**.02**	10 (53)	.44
Epidural and subdural collection (12)	3 (25)	5 (42)	1.0	4 (33)	.55
Epidural and parenchymal collection (3)	1 (33)	0 (0)	.33	2 (67)	.57
Subdural and parenchymal collection (6)	0 (0)	5 (83)	.16	1 (17)	.24
Epidural, subdural, and parenchymal collection (4)	0 (0)	2 (50)	1.0	2 (50)	1.0
Presumed source of infection					
Sinus (78)	17 (22)	29 (37)	.34	32 (41)	.66
Otogenic (8)	2 (25)	2 (25)	.59	4 (50)	.72
Trauma (3)	0 (0)	2 (67)	1.0	1 (33)	1.0
Hematogenous or unknown (17)	1 (6)	8 (47)	.25	8 (47)	.79
Infectious complications					
Dural venous sinus thrombosis (14)	2 (14)	7 (50)	.70	5 (36)	.77
Cavernous venous sinus thrombosis (5)	0 (0)	1 (20)	1.0	4 (80)	.16
Orbital abscess (16)	5 (31)	7 (44)	.51	4 (25)	.17
Osteomyelitis (31)	6 (19)	12 (39)	1.0	13 (42)	1.0
Bacteremia (14)	0 (0)	8 (57)	**.04**	6 (43)	1.0
Co-pathogens					
Any co-pathogen (63)	7 (11)	27 (43)	**.03**	29 (46)	.43
Any co-pathogen except CoNS (51)	6 (12)	21 (41)	.17	24 (47)	.43
MSSA (15)	3 (20)	6 (40)	1.0	6 (40)	1.0
MRSA (2)	0 (0)	0 (0)	NA	2 (100)	.18
CoNS (27)	2 (7)	14 (52)	.06	11 (41)	1.0
Other *Streptococcus* spp (12)	2 (17)	4 (33)	1.0	6 (50)	.76
Other gram-positive aerobes (5)	1 (20)	3 (60)	1.0	1 (20)	.39
Gram-negative aerobes (15)	1 (7)	7 (47)	.25	7 (47)	.78
Gram-positive anaerobes (11)	0 (0)	5 (45)	.16	6 (55)	.52
Gram-negative anaerobes (9)	1 (11)	4 (44)	1.0	4 (44)	1.0
Year diagnosed					
2011 or before (34)	2 (6)	11 (33)	.19	20 (61)	**.02**
2012–2015 (37)	10 (27)	14 (38)	.27	13 (35)	.30
2016 or after (36)	8 (22)	16 (44)	1.0	12 (33)	.21
Source control procedures					
Any (64)	9 (14)	28 (44)	.10	26 (41)	.84
>1 (16)	0 (0)	9 (56)	**.02**	7 (44)	1.0
Restarted IV antibiotics after oral transition (2)	0 (0)	2 (100)	1.0	NA	NA
Loss to follow-up after oral transition (5)	4 (80)	1 (20)	**.04**	NA	NA

Fisher exact test was used to compare patients transitioned to oral therapy at <28 days vs those transitioned at ≥28 days and to compare patients treated with oral therapy vs those treated with exclusive IV therapy. Statistically significant differences ($P < .05$) are shown in bold. One patient was lost to follow-up immediately after discharge and is not included in this table as oral transition is unknown.

Abbreviations: CoNS, coagulase-negative staphylococci; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; NA, not applicable.

Table 3. Patient Laboratory Values Stratified by Treatment Course

Laboratory Data	Transitioned to Oral <28 Days	Transitioned to Oral ≥28 Days	*P* Value (<28 vs ≥28 Days)	All IV Therapy	*P* Value (Any Oral vs IV)
Highest CRP value, mg/L	n = 20; 61 (25–128)	n = 41; 157 (63–254)	**.01**	n = 45; 120 (42–213)	.70
CRP prior to oral transition, mg/L	n = 18; <5 (<5–14)	n = 40; <5 (<5–<5)	**.04**	NA	NA
Highest ESR value, mm/hour	n = 20; 38 (25–68)	n = 40; 77 (44–95)	**.01**	n = 45; 67 (44–92)	.67
ESR prior to oral transition, mm/hour	n = 17; 18 (9–36)	n = 40; 9 (5–18)	**.02**	NA	NA

Data are shown as No.; median (interquartile range) unless otherwise indicated. Wilcox-Mann-Whitney test was used to compare patients transitioned to oral therapy at <28 days vs those transitioned at ≥28 days and to compare patients treated with oral therapy vs those treated with exclusive IV therapy. Statistically significant differences ($P < .05$) are shown in bold. The lowest CRP reported by our laboratory is <5 mg/L; such values were treated as 5 for statistical analysis.

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IV, intravenous; NA, not applicable.

Having at least 1 source control procedure was not associated with treatment group (Table 2). More than 1 source control procedure was done on 16 patients (15%). No patients with multiple source control procedures were treated with early oral therapy compared to 9 of the 41 patients (22%) transitioned later ($P = .02$). Patients diagnosed in 2011 or before were less likely to be transitioned to oral therapy than those diagnosed after 2011 ($P = .02$).

Oral Therapy

Complications associated with IV therapy contributed to 34 (56%) of the 61 oral transitions including peripherally inserted central catheter complications (10 patients [16%]), hematologic abnormalities presumed secondary to an IV antibiotic (19 patients [31%]), and other presumed medication reactions to an IV antibiotic (11 patients [18%]). The most used oral antibiotic was levofloxacin (56 patients [92% of regimens]), followed by metronidazole (47 patients [77%]). Other oral antibiotics included ciprofloxacin (1 patient [2%]), amoxicillin-clavulanate (2 patients [3%]), doxycycline (2 patients [3%]), trimethoprim-sulfamethoxazole (3 patients [5%]), clindamycin (7 patients [12%]), and linezolid (1 patient [2%]). Combination therapy was common, with levofloxacin and metronidazole being used in 45 patients (74%). Five patients (9%) stopped levofloxacin, at least in part due to a presumed drug reaction, including 1 patient with arthralgias.

Levofloxacin dosing varied based on age, with the most common dose being 500 mg/day (used in 32 regimens [57%]). At our center, levofloxacin is commonly dosed at 20 mg/kg/day divided every 12 hours for those <5 years of age, 15 mg/kg/day divided every 12 hours for those 5–10 years of age, and 10 mg/kg daily for children >10 years of age (maximum dose 500 or 750 mg), without specific guidelines for intracranial infections.

Oral Therapy at <14 Days

Seven patients were transitioned to oral therapy prior to 14 days of treatment. Statistical comparisons were not attempted due to the small number of patients. Their ages ranged from 7 to 14 years (median, 11 years). Five (71%) of these patients had an epidural collection, 1 (14%) had a subdural collection, and 1 (14%) had an epidural and subdural collection. Six (86%) infections were presumed to have originated from the sinuses and 1 (14%) was otogenic. Three (43%) were associated with a periorbital abscess and none were associated with dural venous sinus thrombosis, cavernous sinus thrombosis, osteomyelitis, or bacteremia. Four patients (57%) had a coinfection. Identified co-pathogens were MSSA, *Streptococcus mitis*, coryneform bacteria, coagulase-negative staphylococci, and *Fusobacterium* (1 patient each). Three patients (43%) had a source control procedure. Peak CRP ranged from 24 mg/L to 283 mg/L (median, 128 mg/L); peak ESR ranged from 25 mm/hour to 94 mm/hour (median, 42 mm/hour). Median CRP and ESR before oral transition were 30 mg/L (6 patients [range, 5–89]) and 45 mm/hour (5 patients [range, 14–81]), respectively. Patients were treated for a median of 42 days (range, 16–92 days). Two patients were lost to follow-up prior to completion of therapy. No patients were known to have failed oral therapy.

DISCUSSION

Only a single patient out of 61 had worsening of intracranial infection after transition to oral therapy, and this patient did not fill their prescription. Such success is consistent with prior series demonstrating oral transition as early as 2 weeks [24–27]. More recently, a large retrospective study in the United Kingdom showed successful transition to oral therapy in 61 patients, though these were not exclusively *S anginosus* and the details of transition to oral therapy were not the focus of the study [28].

Our typical patient was a middle-school-aged boy with infection presumed to have originated from sinuses, initially treated with ceftriaxone, metronidazole, and vancomycin, consistent with prior studies [12, 29]. Patients transitioned early to oral therapy had less severe infection as evidenced by more frequent epidural infections, less frequent parenchymal infections, less frequent bacteremia, lower peak inflammatory markers, and not requiring more than a single source control procedure. No parenchymal infections were present in those transitioned to oral therapy before 14 days. This reduced severity of infection is also reflected in the total duration of therapy, which was shorter in patients transitioned early to oral therapy compared to those transitioned later. Those transitioned late to oral therapy essentially had normalization of inflammatory markers, whereas those transitioned early (and particularly <14 days), did not

have time for complete normalization of inflammatory markers, suggesting that complete normalization of inflammatory markers is not a prerequisite to oral transition. Most patients showed imaging improvement or resolution of intracranial findings. Notably, 20% of patients with MSSA coinfection transitioned to oral therapy at <28 days, suggesting that MSSA is not a contraindication to early oral therapy. Many patients with MSSA coinfection had targeted antistaphylococcal therapy for a least part of their antibiotic regimen (eg, nafcillin, doxycycline, trimethoprim-sulfamethoxazole, and linezolid). Only 2 patients had MRSA (both treated exclusively intravenously).

Most patients in our study were transitioned to oral therapy, at least in part, due to central line complications or intolerance of an IV antibiotic. Our results suggest that completion of therapy with IV antibiotics is not necessary for many patients, and the risk-benefit consideration may favor transition to oral therapy during their treatment course. Patients transitioned to oral therapy at ≥28 days had a median duration of therapy 33 days longer than those maintained on IV therapy. The reasons for this difference are unclear but may either reflect the use of oral therapy to lengthen total duration or a desire to "compensate" for oral antibiotics with longer a duration. However, as patients in our study on oral therapy did well, such compensation may be unnecessary, and use of oral antibiotics to extend therapy beyond resolution of infection is inappropriate.

Levofloxacin was the most used oral antibiotic in our series. Medical documentation did not provide insight into if other oral medications were considered. Though data are lacking on differential penetration of levofloxacin into epidural, subdural, and parenchymal collections, no difference in outcomes between abscess sites was seen in our series. Levofloxacin has favorable pharmacokinetic and pharmacodynamic characteristics for the treatment of central nervous system (CNS) infections, including those that are deep or parenchymal. The fluoroquinolones are highly orally absorbed and accumulate in multiple tissues, abscesses, and phagocytes at levels above serum concentrations [30–33]. Levofloxacin is lipophilic, which promotes CNS penetration, and high cerebrospinal fluid levels have been demonstrated for both inflamed and noninflamed meninges [34–36]. Levofloxacin is an effective component of treatment regimens for CNS tuberculosis [37–39]. Interestingly, susceptibility to levofloxacin was unavailable for many patients. Though levofloxacin resistance appears rare, requesting susceptibility at the time of diagnosis is prudent if oral transition is anticipated [40, 41].

We make special note of the 2 patients who did require reinitiation of IV therapy after oral transition. While unable to draw conclusions from a single patient, worsening infection in the patient who did not fill their oral prescription suggests that not all patients transitioned to oral therapy would have done well without continued therapy, though as many patients were treated with prolonged IV therapy before oral transition, many may have done well without additional antibiotics. By transitioning to oral therapy, families may be tempted to conclude that the infection is no longer as "serious". This is also suggested by the 5 patients lost to follow-up prior to completion of oral therapy. Therefore, when transitioning to oral therapy, providers should reinforce the importance of adherence and avoid implying that oral transition represents de-escalation. The second patient was restarted on IV therapy due to a presumed reaction to levofloxacin. Intolerance of levofloxacin was uncommon and less frequent than intolerance of IV medications (though challenging to directly compare given difference in duration and drug combinations). Encouragingly, no instances of tendon rupture, adverse mental health effects, or hypoglycemic coma (concerns prompting the US Food and Drug Administration to warn against routine fluoroquinolone use for sinusitis, bronchitis, and urinary tract infection) were documented, though 1 patient had arthralgias.

Generalizability of our findings is limited by the retrospective study design, which introduces inherent selection bias regarding which patients were transitioned to oral therapy. Additionally, as this study was retrospective, there is significant heterogeneity the precise timing of oral transition—for example, between patients with epidural and deeper infections—which prevents a precise determination of when an oral transition can safely occur in all circumstances. We note that many patients completed prolonged IV antibiotics prior to oral transition, and so additional treatment may not have been necessary for many patients transitioned to oral antibiotics, notwithstanding the patient who failed treatment after not filling their prescription. Outcome assessments were further limited by data obtainable from the electronic medical record and represent success through the end of therapy, except for the 5 patients lost to follow-up prior to completion. While most patients had subsequent encounters after therapy completion without evidence of recrudescence of intracranial infection, this was not able to be systematically assessed, so it is possible we did not capture failure after completion of therapy or in the 5 patients lost to follow-up. Likewise, we did not have complete data to assess neurologic outcomes or power to compare patients with uncommon conditions such as MRSA coinfection or cavernous sinus thrombosis.

Other limitations include considering coagulase-negative *Staphylococcus* as a co-pathogen rather than a contaminant with the understanding that interpretation of coagulase-negative *Staphylococcus* is often individualized for a given patient presentation. Additionally, 46 patients (69% of the patients with a source control procedure) received antibiotics at least 1 day prior to source control (median, 1 day [interquartile range, 0–2 days]; high, 39 days). However, as clinicians often determine antibiotic start dates from source control, we believed that this was the most clinically relevant start date. Frequency and median duration of treatment prior to source control was not different between the treatment groups. Finally, data were limited to what was available in the electronic medical record, and information such as

size of initial fluid collection, species-level data of *S anginosus*, and complete susceptibility data were often unavailable.

CONCLUSIONS

Levofloxacin-based oral antibiotic regimens were safe and well tolerated for pediatric intracranial *S anginosus* group infections. Early oral transition was successful for epidural infections, but minimal data were available for parenchymal infections. Early transition to oral therapy should be considered in patients with epidural fluid collections, improving inflammatory markers and imaging, and an uncomplicated neurosurgical course, particularly when a patient is unable to tolerate IV therapy and susceptibility to oral antibiotics is confirmed. Such early transition would spare patients the inherent risk of a central venous catheter, and the effectiveness of such therapy is increasingly supported by literature.

Notes

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Patient consent. The design of the work was been approved by the Colorado Multiple Institutional Review Board and deemed exempt from patient consent due to its retrospective nature.

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Potential conflicts of interest. All authors: No reported conflicts of interest.

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