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ORIGINAL ARTICLE

Serologic Detection of Antibodies Targeting the Leukocidin LukAB Strongly Predicts *Staphylococcus aureus* in Children With Invasive Infection

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Background. *Staphylococcus aureus* is among the most commonly identified causes of invasive bacterial infection in children; however, reliable results from cultures of sterile-site samples often cannot be obtained, which necessitates prescription of a broad empiric antimicrobial agent(s). Children with invasive *S aureus* infection rapidly generate high antibody titers to the cytotoxin LukAB; therefore, the aim of this study was to assess the diagnostic utility of an anti-LukAB antibody assay for children with musculoskeletal infection (MSKI).

Methods. We conducted a 2-year prospective study of all eligible children admitted to Vanderbilt Children's Hospital with an MSKI. Acute and convalescent sera were obtained, and antibodies that target LukAB were measured by an enzyme-linked immunosorbent assay.

Results. Forty-two children were enrolled. The median concentrations of LukAB antibodies for children with *S aureus* infection were 130.3 U/mL in the acute phase and 455 U/mL in the convalescent phase ($P < .001$). The median concentrations of LukAB antibodies in children with a non–*S aureus* MSKI were 8.6 U/mL in the acute phase and 9.7 U/mL in the convalescent phase. The assay discriminated between *S aureus* and non–*S aureus* infection with areas under the receiver operating characteristic curve of 0.81 (95% confidence interval, 0.67–0.95; $P < .001$) and 0.95 (95% confidence interval, 0.86–1; $P < .001$) for samples tested in the acute and follow-up periods, respectively. With no false-negative results, the assay accurately ruled out *S aureus* in samples obtained during the convalescent phase.

Conclusion. Culture-independent diagnostics have the potential to improve care by narrowing antimicrobial therapy on the basis of the likelihood of *S aureus* infection. The results of this proof-of-concept study suggest that a LukAB serologic assay might be useful in the diagnosis of invasive bacterial infections, and larger-scale validation studies are warranted.

Keywords. diagnostic assay; immune response, LukAB, *Staphylococcus aureus*.

Invasive bacterial infections in children, such as bacteremia with end-organ infection (eg, osteomyelitis, septic arthritis, pyomyositis, visceral abscesses), are associated with significant morbidity and death [1]. To identify a causative pathogen, culture or molecular testing of a sterile-site sample is required. In many cases, however, tissue cannot be obtained or testing results are negative, which results in prescription of broad-spectrum antimicrobial regimens [2, 3]. Culture-independent serologic assays can guide management decisions; however, these tests are not readily available or lack sufficient specificity and sensitivity to warrant their routine use in testing for the most common invasive bacterial pathogen in children, *Staphylococcus aureus* [4, 5].

The ability of *S aureus* to elaborate potent cytolytic toxins is essential for its virulence [6]. LukAB, the most recently discovered bicomponent cytotoxin, is produced in abundance by *S aureus* and is a critical component of the organism's ability to subvert the innate human immune response [7–10]. We previously found that LukAB is ubiquitous in invasive clinical isolates and that children with invasive *S aureus* disease generate high serum anti-LukAB immunoglobulin G (IgG) titers early in the course of disease [11].

Although others have investigated the utility of host antibody response in diagnosing invasive staphylococcal infection [12–15], to our knowledge, no studies to date have investigated LukAB as the target antigen. Thus, the primary aim of this study was to evaluate the utility of anti-LukAB antibody detection as a diagnostic assay to predict *S aureus* as the etiologic agent of acute musculoskeletal infection (MSKI).

METHODS

Study Design and Population

We conducted a prospective cohort study of children aged 6 months to 18 years who were admitted to the Monroe Carell

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Jr. Children's Hospital at Vanderbilt between September 2014 and October 2016 with an acute MSKI. Potential study subjects were identified by daily communication with the pediatric infectious diseases and orthopedic surgery consult services. Children were approached for the study if there was a strong clinical suspicion for acute MSKI based on the following symptoms: fever, osteoarticular pain (eg, tenderness to palpation of a joint, bone pain, or refusal to bear weight), and elevated inflammatory marker levels (erythrocyte sedimentation rate or C-reactive protein). Children were excluded from the study if there was clinical evidence suggesting an alternative diagnosis, an inability to obtain informed consent (eg, language barrier), a primary or secondary immunodeficiency, a history of malignancy, bone marrow transplant, or solid organ transplant, or receipt of intravenous immunoglobulin or blood products in the preceding 12 months.

Informed consent from the parents and, when possible, informed assent from the participant were obtained before inclusion in the study. The study was approved by the Vanderbilt University Medical Center institutional review board.

Patient Enrollment

Serum samples were obtained within 48 hours of enrollment (acute sera) and at an outpatient follow-up visit 3 to 6 weeks after hospital discharge (convalescent sera). Sera were obtained by centrifugation of whole-blood samples and stored at −20°C until processing. After enrollment, the subjects were monitored using the Vanderbilt electronic medical record to determine whether a microbiologic diagnosis was ultimately secured by culture. The subjects were grouped according to whether they had a culture-proven *S aureus* infection or infection caused by any other organism. If the culture results were negative, the subject was grouped with the non–*S aureus* infection group, given the propensity for *S aureus* to grow in culture and the high likelihood that cases of culture-negative MSKI are caused by a nonstaphylococcal pathogen (eg, *Kingella kingae*) [16–18]. If a subject did not undergo a drainage procedure or acquisition of a culture specimen from a sterile site (blood, bone, or joint), that subject was excluded from the study. Undergoing antibiotic treatment before samples for culture were obtained did not exclude any patients, and this information was recorded with other clinical data.

Healthy control samples were obtained from pediatric subjects who were undergoing an outpatient procedure at Monroe Carell Jr. Children's Hospital at Vanderbilt for a noninfectious indication, and they were selected if they had no known history of *S aureus* disease of any type and met the eligibility criteria described earlier. Serum samples were obtained from healthy control subjects at the time of enrollment.

Serum Antibody Measurement

The serum antibody response was measured by an indirect enzyme-linked immunosorbent assay against purified dimerized LukAB, as previously described [11, 19, 20] and detailed in Supplementary Methods. Briefly, purified LukAB was bound to 96-well plates, and dilutions of sera were added. LukAB binding was detected by horseradish peroxidase–conjugated murine monoclonal antibodies against human IgG. Samples were run in duplicate, independently on separate days, and a third run was performed if the first 2 titer values differed by ≥1 dilution. Investigators were blinded to the culture results of the samples at the time of the assay. The antibody concentration in each sample was interpolated from a standard curve of a human-derived monoclonal antibody against LukAB [20].

Total IgG Quantification

The total IgG level in each sample was measured by an immunoturbidimetric assay performed at the Vanderbilt University Medical Center clinical laboratory.

Statistical Analysis

Univariate analysis was used to compare the culture-proven *S aureus* and non–*S aureus* (ie, alternative pathogen or negative culture result) infection groups regarding the variables of interest. Independent continuous variables were analyzed with the 2-sample Student t test (normally distributed) or Mann-Whitney U test (nonnormally distributed). Paired samples were analyzed with a paired t test (normally distributed) or Wilcoxon matched-pairs signed-rank test (nonnormally distributed). A χ^2 test was used for nominal variables. Correlation between variables was assessed by the Spearman correlation coefficient (r_s). Logistic regression analysis was performed to evaluate the prediction ability of the model measured by the c statistic (area under the receiver operating characteristic [ROC] curve for a binary diagnosis). Likelihood ratios were reported in lieu of predictive values, because likelihood ratios are independent of disease prevalence [21]. Two-sided *P* values of <.05 were considered statistically significant. Data analysis was performed using R 3.3.0 and Prism 6 for Mac OS X version 6.0e.

RESULTS

Characteristics of the Study Population

During the study period, 54 children were identified with a possible MSKI; 42 met the eligibility criteria and were enrolled in the study (Figure 1). Acute sera were obtained from all the enrolled patients within 48 hours of enrollment, and convalescent sera were obtained from eligible subjects who returned for a follow-up visits/blood draw (28 patients). Of these 42 patients, 41 had both blood and operative cultures obtained; one patient had blood cultures only. The majority of the enrolled patients were male and non-Hispanic white, with a median age of 6.5 years (Table 1). Septic arthritis and osteomyelitis were the most common infection types (43% and 36%, respectively). *S aureus* was the most common pathogen recovered (60%), and 72% of the *S aureus* isolates were methicillin susceptible. No

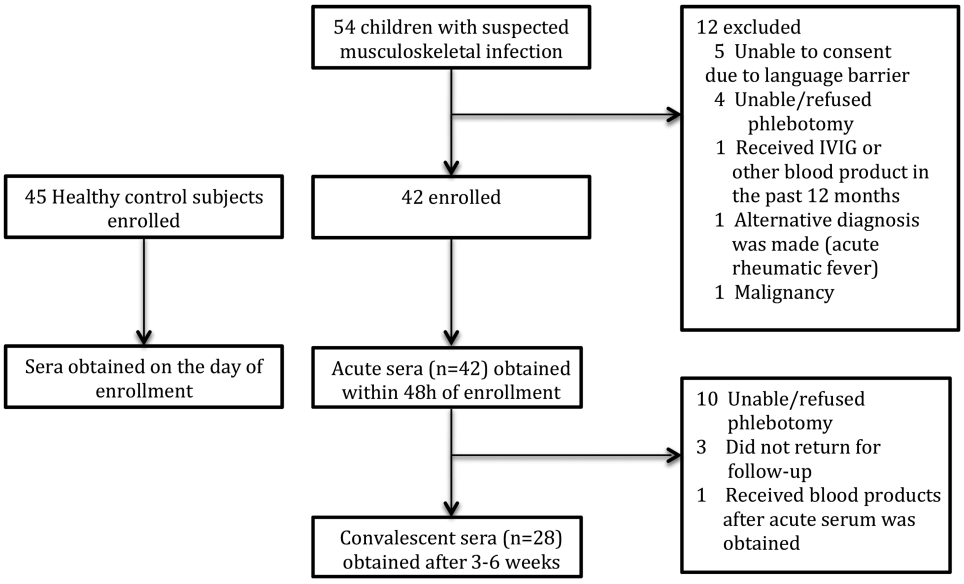

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram. Abbreviation: IVIG, intravenous immunoglobulin.

Table 1. Baseline Characteristics of the Population (N = 42) Studied

Characteristic	Value(s)
Sex (n [%])	
Male	29 (69)
Female	13 (31)
Race (n [%])	
Non-Hispanic white	36 (86)
Non-Hispanic black	5 (12)
Other	1 (2)
Age (median [IQR]) (y)	6.5 (1–11)
Infection type and location (n [%])	
Osteomyelitis	15 (36)
Femur	6
Fibula	2
Tibia	3
Pelvis	2
Vertebrae	2
Septic arthritis[a]	18 (43)
Hip	7
Knee	8
Ankle	1
Elbow	1
Sacroiliac	2
Both	4 (10)
Upper extremity	2
Lower extremity	2
Pyomyositis	5 (12)
Lower extremity	5
Pathogen (n [%])	
Staphylococcus aureus	25 (60)
Methicillin resistant	7
Methicillin susceptible	18
Kingella kingae	4 (10)
Streptococcus pyogenes	2 (5)
Negative culture result (n [%])	11 (24)

Abbreviation: IQR, interquartile range.
[a]One patient had 2 sites affected.

pathogen was recovered (ie, culture results were negative) from the majority of participants in the non-*S aureus* infection group. The most frequently identified pathogens in this group were *K kingae* and *Streptococcus pyogenes*. One of the 11 patients with a culture-negative infection was pretreated with an antibiotic (vancomycin) before tissue sampling.

Compared with those in the non–*S aureus* infection group, children with culture-proven *S aureus* were older, had a higher maximum temperature during hospitalization, and had higher levels of inflammation markers (C-reactive protein, erythrocyte sedimentation rate, and absolute neutrophil count [ANC]; Table 2). We found no significant difference in the mean durations of symptoms before serum collection between the *S aureus* group (6 days) and the non–*S aureus* group (4 days).

Serum was obtained on the day of enrollment from each of 45 healthy pediatric controls. Their median age was 8 years (interquartile range [IQR], 3.5–13 years), and the majority of them were male (55.6%).

Anti-LukAB Antibody Response

The median concentration of antibodies against LukAB in healthy uninfected controls was 70.1 U/mL (IQR, 27.6–121.3 U/mL). In the acute phase, patients with culture-proven *S aureus* infection had a median antibody concentration of 130.3 U/mL (IQR, 81.7–282.5 U/mL), which was significantly higher than that of healthy controls ($P = .006$) (Figure 2A). Patients without apparent *S aureus* infection (the non–*S aureus* infection group) had a median acute-phase anti-LukAB antibody concentration of 8.6 U/mL (IQR, 0.4–110.2 U/mL), which was not significantly different than that in healthy controls and was significantly lower than that in patients with *S aureus* infection ($P < .001$).

Table 2. Clinical Features of *S aureus* and Non–*S aureus* Infections[a]

Characteristic	*S aureus* Infection (N = 25)	Non–*S aureus* Infection (N = 17)	*P* Value[b]
Clinical presentation			
Age (years)	9 (6.5–12)	1 (0.8–4.5)	<.001
Days of symptoms before admission	3 (2–6)	3 (1.5–5)	.276
Days of fever before admission	2 (1–4)	1 (0–4.5)	.273
Maximum temperature before admission[c]	102 (100.8–103)	101.9 (101.3–103.3)	.978
Treated with antibiotics before admission	5 (20)	0 (0)	.078
Able to bear weight at admission[d]	7 (32)	2 (13)	.439
History of SSTI documented[e]	4 (16)	0 (0)	.206
Vital signs[f]			
Temperature at admission (F)	99.5 (98.2–101)	98.8 (98.2–100.1)	.857
Maximum temperature (F)	102.9 (102.1–103.4)	101.8 (99.2–102.7)	.008
Heart rate at admission (bpm)	125 (104–140)	130 (107–141)	.688
Respiratory rate at admission (breaths per minute)	22 (20–25)	27 (21–29)	.027
Laboratory values[g]			
WBC count at admission (cells × $10^3/\mu L$)	12.2 (8.1–16.8)	13.8 (10.7–15.5)	.405
Peak WBC count (cells × $10^3/\mu L$)	12.8 (9.9–17.3)	14.3 (11.2–16.1)	.555
ANC at admission (cells × $10^3/\mu L$)	8.9 (5.6–13)	5.7 (3.8–8.2)	.02
Peak ANC (cells × $10^3/\mu L$)	9.1 (6.1–14.2)	5.7 (4.2–8.5)	.005
Hematocrit at admission (%)	35 (31.5–37)	34 (32.5–36)	.455
Platelet count at admission (× $10^3/\mu L$)	305 (213–405)	420 (333–492.5)	.012
CRP at admission (mg/L)	166.1 (62.5–240.5)	55.6 (20.1–86.9)	.004
Peak CRP (mg/L)	190.6 (93.7–256.6)	73.7 (30–96.4)	.001
ESR at admission (mm/hour)	66.5 (39.5–86)	38 (26–56.5)	.018
Peak ESR (mm/hour)	77 (61–91.8)	38 (26–71)	.002

Abbreviations: ANC, absolute neutrophil count; bpm, beats per minute; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SSTI, skin and soft-tissue infection; WBC, white blood cell.

[a]Data presented are medians (interquartile range) or number (percentage).

[b]*P* values were determined using the independent *t* test for normally distributed data and Mann-Whitney *U* test for nonnormally distributed data.

[c]In those who reported fever.

[d]Three patients in each group were too young to bear weight or had an upper-extremity infection.

[e]Not documented (16 in the *S aureus* group and 12 in the non–*S aureus* group).

[f]Vital signs during hospitalization, unless otherwise noted.

[g]Laboratory values during hospitalization, unless otherwise noted.

In the convalescent phase, patients with *S aureus* had a markedly higher median antibody concentration (455 U/mL [IQR, 226–972.6 U/mL]) than healthy controls ($P < .001$). The non–*S aureus* infection group had a median antibody concentration of 9.7 U/mL (IQR, 0.6–151.7 U/mL) in the convalescent phase, which was not significantly different than that in healthy controls but significantly lower than that in patients with *S aureus* infection ($P < .001$).

We found a significant rise in antibody concentration from the acute to convalescent phase in patients with *S aureus* infection ($P < .001$) but not in the non–*S aureus* infection group ($P = .578$) (Figure 2B). No association was found between duration of symptoms and acute-phase LukAB antibody concentration in patients with *S aureus* infection ($r_s = 0.115$; $P = .583$) or in those with non–*S aureus* infection ($r_s = -0.028$; $P = .915$) (Figure 3). In addition, none of the findings changed when the results were adjusted for the total IgG level per sample (median, 812 mg/dL per sample).

Performance of the Assay

The ability of the LukAB serologic assay to discriminate between those with *S aureus* infection from those without evidence of *S aureus* infection (ie, with an alternative pathogen or negative culture result) was assessed using an ROC curve. The areas under the ROC curve were 0.81 (95% confidence interval [CI], 0.67–0.95; $P < .001$) and 0.95 (95% CI, 0.86–1; $P < .001$) for acute-phase and convalescent-phase samples, respectively (Figure 4). The data were analyzed also after excluding the culture-negative samples (because they were assumed to be from a non–*S aureus* pathogen); no significant differences were seen between the areas under the ROC curve for acute-phase (0.80) and convalescent-phase (1.0) samples.

Using the sensitivities and specificities generated from the ROC analysis, we established positive, negative, and equivocal ranges. Samples with an antibody concentration of >200 U/mL were considered positive, suggestive of *S aureus* infection. Samples with an antibody concentration of <15 U/mL were considered negative, and those with an antibody concentration between 15 and 200 U/mL were considered equivocal. Of the 42 acute-phase samples, 23 (54.8%) were considered equivocal (16 *S aureus* samples, 7 non–*S aureus* samples). Of the remaining samples, 8 of 9 culture-proven *S aureus* samples had a titer higher than the positive cutoff value (sensitivity, 88.9%, [95% CI, 51.8%–99.7%]; positive likelihood ratio, 8.9 [95% CI, 1.4–57.9]), whereas 9 of 10 non–*S aureus* samples (according to culture

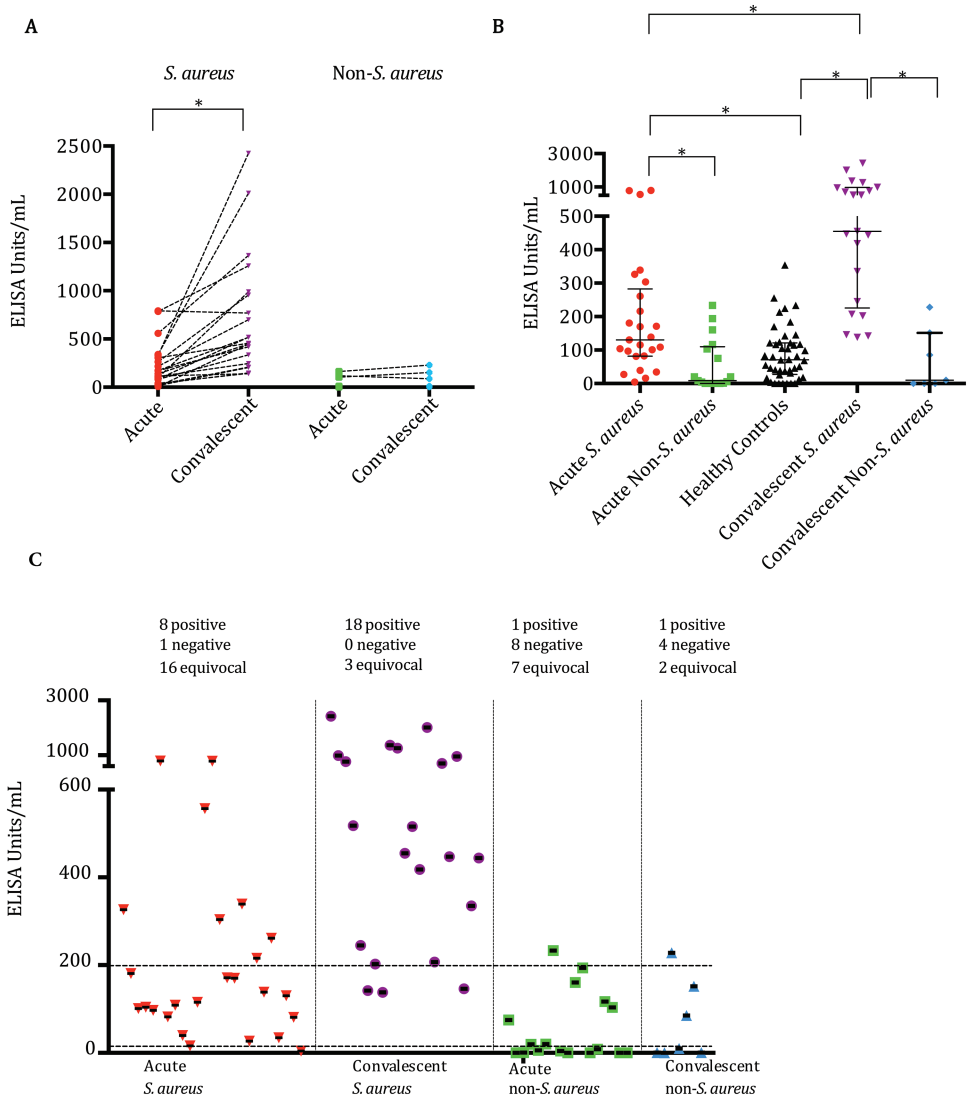

Figure 2. Anti-LukAB antibody concentrations. (A) Median anti-LukAB antibody concentrations and interquartile ranges according to group. The median antibody concentration in patients with *Staphylococcus aureus* infection (acute phase, n = 25; convalescent phase, n = 21) was significantly higher than that in patients with non–*S aureus* infection (acute phase, n = 17; convalescent phase, n = 7) in both phases. The median antibody concentration in the *S aureus* group was higher than that in healthy uninfected pediatric controls (n = 45) in both the acute ($P = .006$) and convalescent ($P < .001$) phases. There was an increase in median antibody concentration in the acute to convalescent phase in the *S aureus* group ($P < .001$) that was not seen in the non–*S aureus* group. (B) Paired samples (acute and convalescent phases) according to group (*S aureus* infection [n = 21] vs non–*S aureus* infection [n = 7]). There was a significant rise in antibody concentration in the *S aureus* group according to a Wilcoxon matched-pairs signed-rank test ($P < .001$). (C) Performance of the enzyme-linked immunosorbent assay (ELISA) with cutoff values established on the basis of results from this cohort and healthy controls. Samples >200 U/mL were considered positive, suggestive of *S aureus* infection; samples <15 U/mL were considered negative, and those in between 15 and 200 U/mL were considered equivocal. Twenty-three of the acute-phase samples were equivocal. Of the remaining samples, 8 of 9 in the *S aureus* group were positive, whereas 9 of 10 non–*S aureus* group samples were below the negative cutoff value. There were 28 convalescent-phase samples, 5 of which were equivocal. Of the remaining samples, 18 of 18 *S aureus* group samples had a titer above the positive cutoff value, whereas 4 of 5 non–*S aureus* culture samples were below the negative cutoff value.

results) were lower than the negative cutoff value (specificity, 90% [95% CI, 55.5%–99.8%]; negative likelihood ratio, 0.1 [95% CI, 0.02–0.8]). We had 28 convalescent-phase samples, 5 (18%) of which were equivocal (3 *S aureus*, 2 non–*S aureus*). Of the remaining samples, 18 of 18 *S aureus*–positive samples had a titer higher than the positive cutoff value (sensitivity, 100% [95% CI, 81.5%–100%]; positive likelihood ratio, 5 [95% CI, 0.9–28.9]), whereas 4 of 5 non–*S aureus* culture samples were lower than the negative cutoff value (specificity, 80% [95% CI, 28.4%–99.5%]; negative likelihood ratio, 0 [95% CI, not calculable because no false-negative results occurred in this group]) (Figure 1C).

DISCUSSION

The major finding of this study is that children with invasive *S aureus* infection generate a high concentration of LukAB-specific

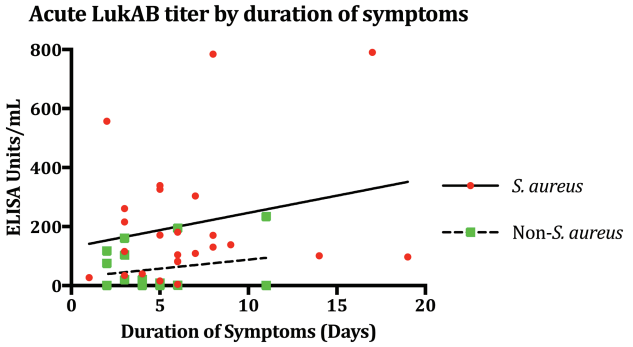

Figure 3. Association between duration of symptoms and acute-phase LukAB antibody titer concentrations. No association between duration of symptoms and acute-phase LukAB antibody concentrations in patients with *S aureus* ($rs = 0.115$; $P = .583$) or non–*S aureus* ($rs = -0.028$; $P = .915$) infection was found. Abbreviation: ELISA, enzyme-linked immunosorbent assay.

antibodies that rise in the convalescent phase; children with non–*S aureus* disease do not generate anti-LukAB antibodies in either phase. As a diagnostic tool, the sensitivity and specificity of the assay were excellent. To our knowledge, this is the first description of the performance of anti-LukAB antibodies as a diagnostic tool.

Current diagnostic modalities require culture or polymerase chain reaction of a sterile-site sample to isolate a causative organism. However, a reliable sterile-site sample is frequently not obtained easily and a pathogen is not identified (eg, MSKI, surgical wound infection, necrotizing pneumonia) [18, 22]. Several reasons for this inability exist, including antibiotic use before sampling, lack of a surgical or drainage procedure, and the fastidious nature of certain organisms in culture. A serologic tool would not be prone to the aforementioned barriers to culture diagnosis and would address a major unmet clinical need.

We evaluated the utility of LukAB antibodies as a diagnostic tool for children with MSKI, because this group represents a relatively homogenous population with one of the most common invasive bacterial infections in children; however, the assay might be a useful diagnostic tool in a variety of common clinical scenarios. In acute phase, a low antibody titer has the potential to be useful in excluding *S aureus* infection in patients in whom the clinical features suggest a non–*S aureus* pathogen but an inability to isolate an alternative pathogen results in the use of empiric antistaphylococcal antimicrobial agents. This situation frequently occurs in younger children with MSKI (eg, for whom *K kingae* is a common pathogen [16, 17], but the fastidious nature of the organism results in negative culture results). Similarly, in critically ill patients (eg, infants with congenital heart disease who become febrile after surgery), a lack of positive culture results often necessitates coverage with vancomycin because of a concern for methicillin-resistant *S aureus* infection. A reassuringly low antibody titer might allow for faster deescalation of potentially harmful antimicrobial agents.

The strong positive predictive value of this assay also provides it utility in cases in which *S aureus* is the likely pathogen but culture results are not reliable. An example of such a situation is a postoperative wound infection, for which *S aureus* is the most common pathogen, but a sterile-site sample for culture cannot be obtained. In this scenario, a high antibody titer could support the use of antistaphylococcal antimicrobial agents and obviate the need for broad Gram-negative coverage, and the performance of this assay warrants evaluation in this setting. As with many serologic assays, the sensitivity of the test increases when convalescent-phase titers are used. In our analysis, the sensitivity increased from 88.9% in acute phase to 100% in convalescent phase. Because the majority of invasive bacterial infections in children, including MSKI, are treated with prolonged courses of antimicrobial therapy [23], serology early in convalescence represents a useful diagnostic opportunity that can alter therapy. Altogether, a reliable serologic assay could assist in the difficult management decisions often encountered regarding children with invasive bacterial infection.

Although it is possible that a LukAB-negative *S aureus* strain can cause invasive disease or that some patients do not produce detectable quantities of antibody against this virulence factor, LukAB is conserved in the *S aureus* genome, and previous studies from our group revealed that, according to a polymerase chain reaction assay, all clinical isolates from children with an

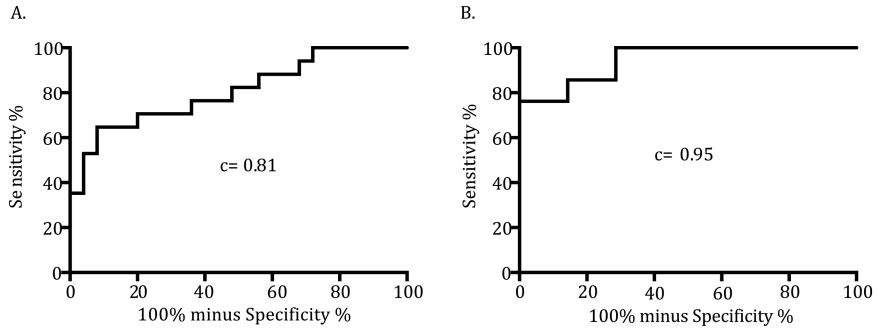

Figure 4. Receiver operating characteristic curve for anti-LukAB antibodies. (A) Acute-phase antibodies exhibited very good discrimination (c statistic, 0.81; $P < .001$). (B) Convalescent-phase antibodies exhibited excellent discrimination (c statistic, 0.95; $P < .001$).

invasive culture-proven *S aureus* infection contained *lukAB* [11, 24]. The results of this study also confirm previous findings from our group that children exhibit a high-titer antibody response early in the course of disease, a time course potentially enhanced by an anamnestic response by previous exposure to the organism, and the significant rise of the antibody concentration in convalescence suggests ongoing LukAB production during invasive disease [11, 24]. To fully understand the kinetics of the anti-LukAB antibody response, a larger (multicenter) study involving samples obtained at more frequent time points is planned. These important findings help illuminate the complex humoral response of children with invasive *S aureus* disease.

Our study had several limitations. It was a single-center study at a major tertiary care children's hospital, and the results might not be generalizable to all populations. Similarly, the assay was tested in children with MSKI, and although results of our previous work suggest that children with other types of invasive infection mount a similar anti-LukAB antibody response [11], the generalizability of it as a diagnostic assay for other invasive infections warrants further clarification. In addition, we classified patients with culture-negative MSKI in the non–*S aureus* infection group given the propensity of *S aureus* to grow in culture when not pretreated with antibiotics, However, this does not definitively prove the absence of *S aureus* as an etiology [16–18]. Important to note, however, is that any classification bias that was produced by the lack of a purely negative reference standard would introduce bias against the assay's performance rather than in its favor, because patients with *S aureus* infection that did not grow in culture would be classified falsely as having a non–*S aureus* infection. Moreover, the performance of the assay did not change significantly in a sensitivity analysis in which patients with culture-negative infection were removed from the data set. In addition, only 28 of the 42 patients returned for follow-up blood testing, which potentially introduced selection bias caused by loss-to-follow-up discrepancies between the 2 groups. It is important to note also that serologic assays cannot distinguish between methicillin-resistant and methicillin-susceptible *S aureus*. Last, the *S aureus* colonization status of healthy control patients was not measured, in part because the lack of colonization at a specific point in time does not rule out recent or intermittent colonization in that subject. However, given that up to 80% of the US population carry *S aureus* at least intermittently [25], it can be assumed that many controls (and subjects with non–*S aureus* infection) had been colonized at the time or recently, which did not seem to affect their anti-LukAB antibody levels.

In an era of rapidly increasing antibiotic resistance and a need for optimal antibiotic stewardship, a clear role exists for an accurate serologic assay for the detection of invasive *S aureus* infection. The results of this proof-of-concept study strongly suggest that the detection of anti-LukAB antibodies represents a promising diagnostic tool for use in children with an invasive bacterial disease such as MSKI. Validation of this assay in a larger multicenter cohort and examination of its potential utility in a predictive model, in conjunction with clinical parameters, is clearly warranted.

Supplementary Data

Supplementary materials are available at *Journal of the Pediatric Infectious Diseases Society* online.

Notes

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Potential conflicts of interests. C. B. C. has performed joint research with or received grants from Pfizer and GSK and has served on scientific advisory boards for Theravance Pharmaceuticals and GSK Vaccines, each of which was outside the scope of the submitted work; V. J. T. is listed as an inventor on patent applications filed by New York University School of Medicine, which are currently under commercial license to Janssen Biotech, Inc; and I. P. T. serves as an investigator on studies funded by GlaxoSmithKline and Horizon Pharma. None of these studies conflict with the contents of this article. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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