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Varicella Hospitalizations and Community-Acquired Methicillin-Resistant *Staphylococcus aureus*: Seven Years of Active Surveillance

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Abstract

Introduction: In Mexico, universal Varicella vaccination is not part of the National Immunization Program. Community-Acquired Methicillin-Resistant Staphylococcus Aureus (CA-MRSA) infection is increasing worldwide. CA-MRSA infection in children with Varicella has scarcely been reported.

Methods and Findings: From January-2012 to December-2018, we performed active surveillance for children <16 years of age hospitalized with Varicella at the Tijuana General Hospital, Mexico. To all patients with suspected bacterial super infection, a culture sampling was conducted. CA-MRSA was described and identified by both in vitro resistance to methicillin and other isoxazolyl penicillins and by identifying the gene mec-A by PCR. A total of 40 patients were enrolled. The median age at admission was 20.5 months (1-190). All but 4 (10%) were previously healthy children. None were vaccinated against Varicella. Cellulitis (with/without abscess) was the leading complication (50%), with 70% CA-MRSA identified in abscesses. Septicemia/bacteremia was present in 10 (25%), blood isolation was confirmed in seven (3 *S. aureus* (all CA-MRSA), 2 *S. pyogenes*, 1 *S. pneumoniae*, 1 *E. coli*).

Conclusion: Hospitalizations by Varicella in our Hospital are not infrequent; they are associated with high morbidity and relatively low mortality. The leading complication was bacterial super infection represented by soft-tissue infections and bacteremia/septicemia mostly due to CA-MRSA.

Keywords: Varicella; Methicillin-Resistant Staphylococcus Aureus (MRSA); Community Acquired Methicillin-Resistant Staphylococcus Aureus (CA-MRSA); Varicella vaccine; Antibiotic control

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Introduction

Varicella is indeed a prevalent and highly contagious infectious disease. Even though it is not associated with high morbidity and mortality, in Latin America (as elsewhere), it may lead to hospitalization due to several types of complications. Some of the complications are bacterial super infections (mainly from soft tissue), meningitis, encephalitis, hepatitis, purpura, among others [1-3].

In Mexico, Universal Varicella Vaccination (UVV) is not part of the National Immunization Program (NIP). Nevertheless, few Mexican studies have shown that by estimating disease burden from seroprevalence (proving that is highly prevalent), vaccination is cost-effective [4,5].

This research is the first prospective study (using active surveillance) of children hospitalized with Varicella in Mexico. Besides, the Tijuana, Mexico–San Diego, USA border region is daily the highest transited globally, with up to 300,000 people crossing this frontier, leading to several binational health implications [6] and consequent highly significant health issues.

Moreover, Community-Acquired Methicillin-Resistant *Staphylococcus Aureus* (CA-MRSA) is increasing worldwide. However, no other publications have shown the association of Varicella complicated with CA-MRSA, except for French National study conducted before France implemented UVV for all children [7].

Methods

From January-2012 to December-2018 (seven years), we performed active/prospective surveillance for children <16 years of age admitted with Varicella at the Tijuana General Hospital. Diagnosis of Varicella was based on the CDC-clinical case definition [1].

We performed culture sampling on all patients with suspected bacterial super infection (in soft tissue with abscess formation, blood, and/or other body sites when indicated). Both spinal tap (for cytochemical analysis and bacterial cultures) and Computerized Tomography (CT scan) was done on all patients admitted with neurologic signs/symptoms.

For Staphylococcus aureus strains, methicillin resistance was identified by either using 6 µg/ml of oxacillin in Mueller-Hinton agar supplemented with 4% NaCl or by PCR detecting the mecA gene. The reaction protocol was as follows: an initial FastStart DNA Taq polymerase activation phase at 95° C for 10 min; a 45-cycle amplification phase consisting of a 95°C segment for 10 s, a 50°C segment for 10 s, and a 72°C segment for 20 s; a melt phase from 45°C to 75°C with a temperature transition rate of 0.1°C/s; and a rapid cooling phase.

The presence of amplified DNA was measured by detecting energy emitted at 640 nm (for the presence of the mecA gene). The temperature at which the hybridization probes dissociated from the target sites was determined by melting curve analysis, as provided by the LightCycler® software (Roche Molecular Systems, Belmont, California, USA), this served as an independent indicator of the specificity of hybridization. Furthermore, we also identified CA-MRSA by presenting *in vitro* resistance to methicillin and other isoxazolylpenicillins.

To detect and confirm the pathogen from the only pleural fluid sample, we grew by conventional culture the pathogen, resulting in *S. pneumoniae*. We confirmed its pneumococcal specific serotype using the Quellung reaction (Statens Serum Institute®, Copenhagen, Denmark).

Following hospital discharge, all patients (who did not die) were followed at the infectious diseases and neurology outpatient clinic looking for potential sequelae.

All captured data was descriptively analyzed by using Excel®

Results

A total of 40 patients were enrolled. Median age at admission was 20.5 months (1-190), with 29 (72.5%) <5 years. All but 4 (10%) were previously healthy children. Two children were immunocompromised, one with Acute Lymphoblastic Leukemia (LLA) and the other with HIV/AIDS. None were vaccinated against Varicella.

Cellulitis was the leading complication seen (20= 50%), from which 15 progressed to abscess formation, and 10 required surgical drainage. From all ten drained abscesses, bacterial isolation was obtained in 100% of cases, with *S. aureus* identified in 7 (all were CA-MRSA) and S. pyogenes in 3.

Neurologic complications manifested as Encephalitis/Meningitis (13=32.5%) were the second cause of complication and eight developed seizures. Bacterial septicemia/bacteremia was present in 10 (25%), blood isolation was confirmed in seven (*3-S. aureus (all CA-MRSA), 2-S. pyogenes, 1-S. pneumoniae, 1-E. coli*).

Other complications were Hemorrhagic Varicella (5=12.5%); Anicteric hepatitis (4=10%); and Pneumonia with Pleural Empyema (1=2.5%, caused by *S. pneumoniae* serotype 18C).

All patients but one received Intravenous (IV) acyclovir, and 29 (72.5%) more than one IV antibiotic (72.4% clindamycin, 51.7% vancomycin, 62% ceftriaxone, and 6.9% meropenem), as well as several other medications. Median hospitalization days were 8 (1-62).

Two patients died (5%), both of septic shock by S. aureus (all CA-MRSA). Among deceased children, one had LLA, while the other child was previously healthy.

Following three months of discharge, 5 patients had sequelae (3 neurological and 2 with severe skin scars) (Figures 1 and 2).

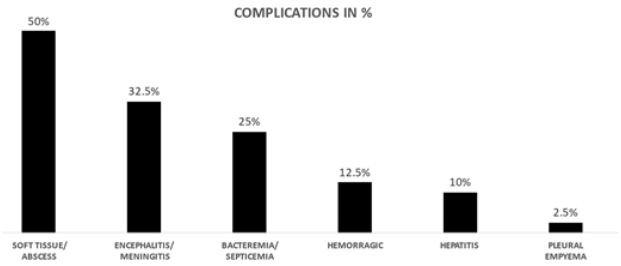

Figure 1 Varicella complications (n=40 total cases).

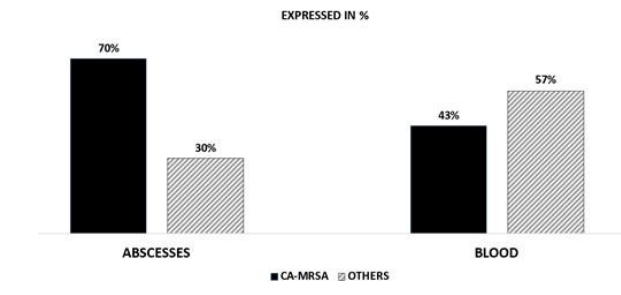

Figure 2 Bacterial Isolation from soft tissues abscesses and blood.

Discussion

Hospitalizations by Varicella in our Hospital are not uncommon (5.7 per year). They are associated with high morbidity, hospitalization days, and treatment, with relatively low mortality.

Bacterial super infection, mainly soft-tissue infections, and bacteremia/septicemia were the leading complications, mostly due to S. aureus (all CA-MRSA), followed by Encephalitis/ Meningitis, hemorrhagic Varicella, and others.

It is also relevant to address that all but two patients from our data were previously healthy children, which one of them died from septic shock by CA-MRSA.

Following other Mexican National and Latin American publications, our data strongly suggest UVV is imperative [2,3,5]

Additionally, our recent presentation showing a much better estimate of both Varicella disease and economic burden, as well as a cost-benefit and cost-effectiveness of UVV in Mexico, strengthens significantly the need for UVV implementation in the country [5].

CA-MRSA has lately been an increasing pathogen threat in many areas of the Globe associated with high morbidity and hospitalizations costs, and even mortality [8,9]. As mentioned before, our study is the second globally describing Varicella and super infection by CA-MRSA just followed by a French publication [7].

Conclusion

1. Following seven years of active/prospective surveillance, Varicella hospitalization may be frequent in previously healthy children in Tijuana, Mexico.
2. The leading complication was super infection by CA-MRSA
3. Both universal Varicella vaccination and better antibiotic use and control are mandatory in our region.

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