Varicella skin complications in childhood: a case series and a systematic review of the literature

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Abstract:

**Background.** Although varicella has usually an uncomplicated course in early childhood, several complications may occur. **Methods.** We conducted a study to review the type and the rate of varicella skin complications in a case series of hospitalized immunologically healthy children over a 9 year period. We also systematically reviewed data from the literature to estimate the rate of varicella skin complications. **Results.** In our case reports, the proportion of skin complications among all those hospitalized for varicella was of 16.4% (CI 13%-20%). The pooled prevalence of skin complications resulting from the systematic review of the literature identifies the likelihood of such complications in the range of 15%-25%. **Conclusions.** Although skin complications of chickenpox generally do not result in permanent sequelae, they may represent determinants of hospitalization and of other indirect costs. The obtained results may be useful for estimating costs associated with hospitalization from varicella in cost-benefit analysis for immunization.

**Keywords:** varicella; skin complications; children
Background
Varicella is an acute, febrile, exanthematous, and highly infectious disease that mostly occurs in childhood. Although usually self-limiting, varicella can result in complications that may require hospitalization, including secondary bacterial infection, respiratory distress and neurological deficits. The range of complications was thought to depend on the immune status and underlying diseases, such as chronic cutaneous or pulmonary disorders and immunosuppressive therapies. Immunocompromised individuals, especially those with T-cell defects, are at increased risk of dissemination of the virus to the internal organs, including lungs, liver, brain, heart, and kidneys. However, healthy individuals may experience complications as well. (1-3)
Skin complications may include cellulitis, abscess, necrotizing fasciitis, impetigo and gangrena. Many studies reported variable rates of skin complications in children affected by varicella, from 2.6% to 41.2%. (4, 5)

We conducted a study to review the type and the rate of varicella skin complications in a case series of hospitalized immunologically healthy children over a 9 year period. We also systematically reviewed data from the literature to estimate the rate of varicella skin complications.

Materials and methods
We retrospectively reviewed the medical records of children 0-18 years old admitted into Bambino Gesù Hospital, Rome, Italy (OPBG), for varicella between 1st January 2004 and 1st January 2013. According to literature, the diagnosis of varicella was based on clinical evidence of characteristic skin lesions in varying stages of development and resolution. Patients with immunodeficit, such as HIV or children with a transplanted organ, were excluded. Immunocompromising condition was defined as any congenital or acquired immunodeficiency, malignancy or receipt of corticosteroids or chemotherapy within 30 days before the onset of varicella. We defined a skin complication for the purpose of this study as an unfavorable skin evolution occurring within 14 days of onset of varicella and to which varicella-zoster virus infection may have contributed in some measure. Consensual definitions of secondary bacterial skin complications came from textbooks and dictionaries.

To estimate the incidence of skin complication from the literature, a MEDLINE search was performed using the keywords “varicella” and “complications” [Subheading] as MESH terms. The results were limited to English publications relevant to paediatric age (0-18 years). We also limited the results to articles published in the time period between January 2003 and January 2013. We
scanned the references of all included articles for additional relevant studies. Inclusion criteria were: 1) cases of varicella in pediatric age; 2) reported case definition for skin complications; 3) skin complications reported with clear numerators and denominators. We excluded reports: 1) if they did not refer the exact number of skin complications in varicella in a well defined study period study; 2) if they were limited to immunocompromised children or to children affected by underlying diseases; 3) if they were case reports or if the study population was limited to adults; 4) if they reported data on both adults and children, not analyzable separately; 5) if they included both hospitalized and not hospitalized children; 6) if they focused only on a specific skin complication.

From each selected article we derived the total number of varicella cases and the number of cases with skin complications. We pooled the estimates of rates and their 95% confidence intervals (CI) by using standard meta-analytic techniques. Data were analyzed using Metanalysis 3 and a pooled estimate of varicella complications incidence was calculated by using a random-effects model with inverse-variance weighting by using the Der-Simonian and Laird method. Statistical heterogeneity was measured by using the chi square test for heterogeneity.

**Results**

**Case series**

We reviewed 431 cases of varicella admitted into OPBG between 1st January 2004 and 1st January 2013. Varicella cases exhibited a regular seasonal distribution reaching their peak during spring. The mean age was of 3.19 years (range 14 days-17.5 years). A similar proportion of varicella cases occurred in males and in females (57.4% and 42.6%, respectively).

Of the enrolled patients, 6 (1.5%) presented with herpes zoster lesions. Their age was in the range of 3.7-15.1 years (mean 10 years).

In our case series, skin complication were identified in 71 out of 431 patients (16.4%; 95% CI: 13%-20%). Some patients had more than one skin infection. The most frequent complications were impetigo in 50 patients (70.4%), cellulitis in 20 (28%) and abscess in 5 (7%). No fasciitis, scarlet fever, staphylococcal scalded skin syndrome, varicella gangrenosa and felon were registered. The mean age of patients affected by skin complications was of 2.67 years (range 2 months-10.5 years).

The highest frequency of cases was observed in children from 1 to 5 year of age (53.5%). As for the others, 21 (29.5%) were younger than 1 year, 11 (15.5%) were aged 5–10 years and just 1 was over over 10 years. Patients had a normal immunological status, verified through immunoglobulin and T subset cells count. A similar proportion of varicella cases occurred in males and in female (52.2% and 47.8%, respectively). The median length of hospital stay was 8.5 days. Fifty-four patients (76%) were treated with intravenous acyclovir and all patients received intravenous antibiotic
therapy because of a bacterial cutaneous superinfection. No sequelae were expected at discharge and no patients died.

**Systematic review**

We examined a total of 259 manuscripts resulting from our MEDLINE search or from additional references found during review. Out of them, 18 studies were eligible for inclusion in the meta-analysis and were analyzed to estimate a pooled rate of skin complications in pediatric age. (1,18)

We excluded 241 articles for the following reasons: 1) they did not report the exact number of skin complications in varicella in a well defined study period study (132); 2) they were limited to immunocompromised children or to children affected by underlying diseases (9); 3) they were case reports (71); 4) the study population was limited to adults (5); 5) they reported data on both adults and children, not analyzable separately (2); 6) they included both hospitalized and not hospitalized children (5); 7) they focused only on a specific skin complication (13); 8) their inclusion criteria were too strict (3) (one report included only children younger than one year, one report only previously vaccinated patients and one report only skin infections complicating congenital varicella syndrome). Finally, one study was excluded because the same date were reported in a previous report of the same author.

The pooled prevalence of skin complications of varicella is reported in Figure 1. There was substantial heterogeneity among the studied included in the analysis (P<0.001).

**Discussion**

Bacterial superinfection of skin lesions are known to occur mostly in infants and toddler and can led to disfiguring scars. The skin with varicella lesion is likely the portal of entry of either Staphylococcus Aureus or Group A Streptococcus. Indeed, infants represent a vulnerable risk group for developing invasive skin complications, particularly during the first two weeks of disease. Most often hospitalization is not needed. Nevertheless, in the event of severe infection, varicella can complicate with cellulitis, abscess, fasciitis and can require hospitalization.

We analyzed the rate of skin complications in hospitalized children with varicella and we compared our results to previous reports. No other comparative incidence figures of varicella skin complications over the world have been published. In our case reports, the proportion of skin complications among all those hospitalized for varicella was of 16.4% (CI 13%-20%).

Reviewing the incidence of varicella skin complications in scientific published reports, the proportion is similar to those described by other authors, as shown by the performed metanalysis. In fact, in revised literature skin complication incidence lies within the CI of 15%-25%. Figure 1.
variation of the proportion of complications from 2.6 to 41.2%, which is reported in literature may depend on the characteristic of the study population (age, underlying diseases, etc) and the methodology of the published reports. In fact, almost every study adopted different inclusion and exclusion criteria. For example, some studies excluded immunocompromised children, some others analyzed patients with underlying diseases separately from healthy children and some others considered all children, independently from their immunological status. (2,6,18) In few reports, varicella skin complication rate was low, while other complications, such neurological ones, were the most frequent diagnoses leading to hospitalization. (4, 10) On the opposite, in few others, the incidence of varicella skin complications was extremely elevated, compared to median results. (3, 5) This finding might be also related to differences in the sociodemographic structure of populations or to a broader availability of outpatient skin-infection treatments by experienced pediatricians and office-based instruction of parents concerning hygienic measures. The different varicella-related hospitalization due to skin complication rates may be also correlated to different hospitalization policies. An high observed rate may reflect the tendency of paediatricians to hospitalize young children for prescribing either antibiotic or antiviral intravenous treatment. We observed that, out of varicella skin complications, cutaneous superinfection was the leading reason for hospitalization. This is in accordance with previous studies in which impetigo was the first cause of hospital admission as well. (9,15)

Conclusions
Epidemiological information on varicella complications in children is essential for the development of appropriate immunization recommendations.

Our study confirms that VZV can cause soft-tissue complications in immunocompetent children, giving rise to manifestations that may require hospitalization. The results of our study are concordant with previous reports, although direct comparison was often difficult due to differing case ascertainment, case definitions, inclusion and exclusion criteria. The obtained results may be useful for estimating costs associated with hospitalization from varicella in cost-benefit analysis for immunization. In fact, varicella affects not only individuals but also society, as the costs of medical care and work days missed by parents combine into a substantial financial burden.
Competing interests
The authors declare no competing interests.

Authors’ contributions
Elena Bozzola analyzed clinical data of patients;
Mauro Bozzola revised literature on varicella skin complications;
Alberto Eugenio Tozzi conducted epidemiological analysis;
Annalisa Grandin collected medical records of patients;
Alberto Villani analyzed clinical data of patients.
References


Figure 1. Prevalence of varicella skin complications

<table>
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<tr>
<th>Study</th>
<th>Prev (95% CI)</th>
<th>% Weight</th>
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<tr>
<td>Bonhoeffer, 2005</td>
<td>0.25 (0.15, 0.36)</td>
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<td>Koturoglu, 2005</td>
<td>0.21 (0.17, 0.24)</td>
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<td>0.20 (0.17, 0.24)</td>
<td>5.49</td>
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<tr>
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<td>0.20 (0.17, 0.24)</td>
<td>5.49</td>
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<td>0.20 (0.17, 0.24)</td>
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<td>Overall</td>
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Q=510.21, p<0.00, I²=96%