PIMS/MIS-C
Au cours de la pandémie de Covid-19

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DES/C de Pathologie infectieuse et tropicale

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COVID-19 in hospitalized children

- Mild disease
- Death extremely rare
- Fever, mild respiratory symptoms
- Very rarely severe pneumonia
- PIMS-TS / MIS-C

397 Children hospitalized (60 French hospitals, Feb-Jun 20) with SARS-CoV-2 infection in France

Kawasaki-like syndrome
April-May 2020
Alert on Myocarditis, shock, Kawasaki disease in children
Geographic Distribution of cases

Which name?

- KD-SARS-CoV2, Kawa-COVID-19, Kawasaki-like multisystemic syndrome
- Paediatric inflammatory multisystem syndrome temporarily associated with SARS-CoV-2: PIMS-TS
- SARS-CoV-2 related multisystem inflammatory syndrome in children: MIS-C

From WHO data, Feb 2021; Sancho-Shimizu J Exp Med
Multisystemic acute vascularitis aigue in children < 5 years

Typical/complete form: fever > 4 days + at least 4 criteria among 5 major:
- Cervical lymphadenopathy > 1.5 cm +, extremities changes, Bilateral bulbar conjunctival injection
- Lips and oral cavity changes, rash

Minor criteria
- Irritability
- Perineal or face desquamations
- Arthralgia
- Vomiting
- Otitis, Aseptic leucocyturia
- Inflammatory markers

Complications
- Seritis, Myocarditis, shock syndrome, Coronary abnormalities

Long-term complication: coronary dilatation/aneurysm
- Risk 23%, but falls to 4% if proper treatment!
Association between SARS-CoV-2 infection and Kawasaki-like multisystem inflammatory syndrome: a retrospective matched case–control study, Paris, France, April to May 2020

MIS-C: 27-fold higher odds of previous exposure to SARS-CoV-2
PIMS Epidemiology in France

Hospitalized COVID-19 cases (all ages)

2-4 weeks after COVID-19 waves (hospitalizations)
Population 21 children
- Contact with a confirmed case 4-6 sem before symptoms
- Positive anti-SARS-CoV-2 IgG antibodies (+ positive PCR: 30%)
- All had fever + meeting definition for Kawasaki disease
- Some had coronary abnormalities (#20%)

Specificities compared to historical KD:
- Older: median age 8.2 vs. 4.0 yrs, p < 0.001
- Almost all had acute abdominal pain (surgical abdomen): OR 84 [4.9–1456]
- Neurological disorder (meningitis/encephalitis): OR 7.3 [1.9–27.7]
- Shock (vasoplegic or cardiogenic): OR 13.7 [4.2–45.1]
- Myocardial dysfunction and markers of myocarditis (tropo, BNP): OR 387 [38–3933]
- Higher levels of inflammatory parameters: C-reactive protein, procalcitonin, ferritin
- Lower lymphocyte cell count
A Proposed Framework and Timeline of the Spectrum of Disease Due to SARS-CoV-2 Infection
Illness Beyond Acute Infection and Public Health Implications

**Figure. Proposed Population-Based Framework for Symptomatic SARS-CoV-2 Infection**

<table>
<thead>
<tr>
<th>Symptom onset</th>
<th>Week 2</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute infection (COVID-19)</strong></td>
<td><strong>Postacute hyperinflammatory illness</strong></td>
<td><strong>Late sequelae</strong></td>
</tr>
<tr>
<td>Characterization</td>
<td>Dysregulated host response</td>
<td>Pathophysiological pathways proposed but unproven</td>
</tr>
<tr>
<td>Active viral replication and initial host response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Gastrointestinal, cardiovascular, dermatologic/mucocutaneous, respiratory, neurological, musculoskeletal symptoms</td>
<td>Cardiovascular, pulmonary, neurological, psychological manifestations</td>
</tr>
<tr>
<td>Fever, cough, dyspnea, myalgia, headache, sore throat, diarrhea, nausea, vomiting, anosmia, dysgeusia, abdominal pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory tests</td>
<td>Viral test (+/-)</td>
<td>Viral test and antibody profile uncharacterized</td>
</tr>
<tr>
<td>Viral test (+)</td>
<td>Antibody (+) after 2 wk</td>
<td></td>
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</tbody>
</table>

Postacute Forms
• First-line therapy for all children is **intravenous immunoglobulins (IVIG)**
• 2 g/kg, can be administered in a single or divided dose depending on the clinical picture and cardiac function
• A second dose of intravenous immunoglobulin might be considered
• **High risk children/severe or IVIG resistance**: methylprednisolone 2-10mg/kg daily
• Etude retrospective
• issue des notifications nationales : Santé publique France
• CRF information médicale
• Analyse de type score de propension

IGIV + methylprednisolone vs. IVIG alone

Non randomisation: risque de biais d’indication
Ex. : « on traite de façon plus intensive un patient plus grave »
Principe: pour chaque patient, on établit une probabilité/score (PS) de recevoir le traitement 1 ou 2 en fonction de ses caractéristiques initiales

- On apparie ces patients en fonction de ce score
- On ajuste sur le poids de la caractéristique initiale « overlap weighting »
  - Différence de poids (moyenne) des caractéristiques entre les 2 groupes de traitement divisé par écart type
  - On vérifie le poids de la caractéristique avant / après ajustement

Thomas L, JAMA 2020
• 2 groupes: IVIG vs. IVIG + corticoides
• Patients PIMS/MISC selon les définitions OMS

• Critère de jugement principal:
  • Persistance de fièvre 48h après le traitement ou recrudescence thermique dans les 7 jours qui ont suivi le traitement

• Critère de jugement secondaire:
  • Nécessité 2e ligne
  • Support hémodynamique
  • Défaillance cardiaque
  • Durée hospitalisation en réanimation
Table 2. Primary and Secondary Analyses in the Propensity Score–Matched Cohorts

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>After propensity score matching</th>
<th>Absolute risk difference between groups (95% CI) [reference: IVIG alone]</th>
<th>Odds ratio (95% CI) [reference: IVIG alone]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVIG and methylprednisolone (n = 32)</td>
<td>3 (9)</td>
<td>-0.28 (–0.48 to –0.08)</td>
<td>0.25 (0.09 to 0.70)</td>
<td>.008</td>
</tr>
<tr>
<td>IVIG alone (n = 64)</td>
<td>24 (38)</td>
<td></td>
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<tr>
<td>Primary outcome</td>
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<tr>
<td>Treatment failure&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Secondary outcomes</td>
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</tr>
<tr>
<td>Second-line treatment&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 (9)</td>
<td>-0.22 (–0.40 to –0.04)</td>
<td>0.19 (0.06 to 0.61)</td>
<td>.004</td>
</tr>
<tr>
<td>Hemodynamic support&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>2 (6)</td>
<td>-0.17 (–0.34 to –0.004)</td>
<td>0.21 (0.06 to 0.76)</td>
<td>.01</td>
</tr>
<tr>
<td>LVEF &lt;55%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2/12 (17)</td>
<td>-0.18 (–0.35 to –0.01)</td>
<td>0.20 (0.06 to 0.66)</td>
<td>.007</td>
</tr>
<tr>
<td>Duration of PICU stay, median (IQR), d</td>
<td>4 (2 to 5)</td>
<td>Reduction of days: –2.4 (–4.0 to –0.7)</td>
<td></td>
<td>.005</td>
</tr>
</tbody>
</table>
Figure 2. Association Between First-line Therapy Group and Treatment Failure Depending on Age and Acute Left Ventricular Dysfunction

<table>
<thead>
<tr>
<th></th>
<th>IVIG and methylprednisolone</th>
<th>IVIG alone</th>
<th>After PS weighting, %</th>
<th>Absolute risk difference between groups (95% CI)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
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<tr>
<td>&lt;10</td>
<td>2/17 (12)</td>
<td>22/39 (56)</td>
<td>52</td>
<td>-0.41 (-0.75 to -0.07)</td>
<td>0.12 (0.02 to 0.62)</td>
</tr>
<tr>
<td>≥10</td>
<td>1/17 (6)</td>
<td>15/33 (45)</td>
<td>40</td>
<td>-0.34 (-0.66 to -0.03)</td>
<td>0.08 (&lt;0.01 to 0.57)</td>
</tr>
<tr>
<td><strong>Ventricular dysfunction</strong></td>
<td></td>
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<tr>
<td>Absent</td>
<td>1/12 (8)</td>
<td>26/44 (59)</td>
<td>45</td>
<td>-0.37 (-0.73 to -0.02)</td>
<td>0.12 (0.01 to 0.93)</td>
</tr>
<tr>
<td>Present</td>
<td>2/22 (8)</td>
<td>11/28 (39)</td>
<td>28</td>
<td>-0.19 (-0.46 to 0.08)</td>
<td>0.27 (0.04 to 1.35)</td>
</tr>
<tr>
<td>All patients</td>
<td>3/34 (9)</td>
<td>37/72 (51)</td>
<td>38</td>
<td>-0.27 (-0.49 to -0.05)</td>
<td>0.17 (0.04 to 0.61)</td>
</tr>
</tbody>
</table>

P value: .02, .03, .05, .14, .01
Bithérapie fait mieux que monothérapie, mais ce ne sont pas des essais randomisés (possibles biais)
CONCLUSIONS
Among children and adolescents with MIS-C, initial treatment with IVIG plus glucocorticoids was associated with a lower risk of new or persistent cardiovascular dysfunction than IVIG alone. (Funded by the Centers for Disease Control and Prevention.)

CONCLUSIONS
We found no evidence that recovery from MIS-C differed after primary treatment with IVIG alone, IVIG plus glucocorticoids, or glucocorticoids alone, although significant differences may emerge as more data accrue. (Funded by the European Union’s Horizon 2020 Program and others; EATS ISRCTN number, ISRCTN69546370.)
Physiopathologie du PIMS?

- Dérégulation immunitaire

**Med**

Clinical and Translational Article

A monocyte/dendritic cell molecular signature of SARS-CoV-2-related multisystem inflammatory syndrome in children with severe myocarditis

**CORONAVIRUS**

Polyclonal expansion of TCR Vβ 21.3+ CD4+ and CD8+ T cells is a hallmark of multisystem inflammatory syndrome in children

**SCIENCE IMMUNOLOGY | RESEARCH ARTICLE**
Conclusion

• Association between COVID-19 and these Kawasaki-like syndromes
  • 2 weeks after adults peaks COVID-19
  • Cases: 4-6 weeks after mild COVID-19 symptoms or contact with SARS-CoV-2

Lessons from FHU teams experiences

• The name (Kawa, PIMS, MIC…) is not important, the child health is important!
• Recognize quickly+++ (do not wait for 5 days of fever!)
  • Some have « incomplete forms » of KD
  • Gastro-intestinal symptoms can be inaugural
  • Troponin, BNP + call the cardiologist: systematic!
• Treat well …
  • … But do not miss another diagnosis. severe bacterial infection (e.g. meningitis)!
### Definitions

<table>
<thead>
<tr>
<th>World Health Organization</th>
<th>Royal College of Paediatrics and Child Health (United Kingdom)</th>
<th>Centers for Disease Control and Prevention (United States)</th>
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<tbody>
<tr>
<td>Children and adolescents 0-19 y of age with fever &gt;3 d AND 2 of the following:</td>
<td>A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP, and lymphopenia) and evidence of single or multiorgan dysfunction (shock, cardiac, respiratory, kidney, gastrointestinal, or neurological disorder) with additional features (see listed in Appendix in Supplement 2). This may include children fulfilling full or partial criteria for Kawasaki disease* Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice) SARS-CoV-2 PCR test results may be positive or negative</td>
<td>An individual aged &lt;21 y presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (&gt;2) organ involvement (cardiac, kidney, respiratory, hemato logic, gastrointestinal, dermatologic, or neurological) Fever &gt;38.0 °C for ≥24 h or report of subjective fever lasting ≥24 h Laboratory evidence including, but not limited to, ≥1 of the following: an elevated CRP level, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, lactate dehydrogenase, or IL-6; elevated neutrophils; reduced lymphocytes; and low albumin AND No alternative plausible diagnoses AND Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test, or COVID-19 exposure within the 4 wk prior to the onset of symptoms Additional comments Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection</td>
</tr>
<tr>
<td>1. Rash or bilateral non purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet)</td>
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<td>2. Hypotension or shock</td>
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<tr>
<td>3. Features of myocardial dysfunction, pericarditis, vasculitis, or coronary abnormalities (including ECHO findings or elevated troponin/NT-proBNP)</td>
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<td>4. Evidence of coagulopathy (by PT, APTT, elevated D-dimers)</td>
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<tr>
<td>5. Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain) AND Elevated markers of inflammation such as ESR, CRP, or procalcitonin. AND No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes. AND Evidence of COVID-19 (RT-PCR, antigen test, or serology positive), or likely contact with patients with COVID-19 Consider this syndrome in children with features of typical or atypical Kawasaki disease or toxic shock syndrome</td>
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