


SARS-CoV-2 tropism across the upper aerodigestive tract

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Sir,

Pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) is related to epithelial expression of angiotensin-converting enzyme II (ACE2) that plays a pivotal role in regulating viral entry. ACE2, a type 1 membrane-bound enzyme located in different epithelial tissues, is involved not only in blood pressure regulation by acting on the renin-angiotensin system, but it is also involved in inflammation and neuro-degeneration.¹ This relationship would be exerted by the SARS-CoV-2 spike (S)-protein, and requires cleavage by TMPRSS2 proteases. Testing ACE2 tissue specificity, Shafiee S et al.¹ reported a medium/high expression for respiratory nasopharyngeal epithelial cells, a medium expression for squamous oral epithelium, a medium/high expression for salivary glandular cells, and a medium expression for lymphatic/squamous tonsillar cells.¹

With regard to ACE2 tissue expression, new studies reported conflicting results: Hikmet et al.² documented consistent localizations to non-respiratory subsites (gut microvilli), while no reliable data exist supporting any detectable expression in the lungs/respiratory epithelium. A high ACE2 expression was detected in esophagus cells and enterocytes, suggesting that SARS-CoV-2 can actively replicate here, and this is consistent with the detection of viral RNA in stools and anal swab of COVID-19 patients.

Gastro-intestinal manifestations have been reported in children and, different from respiratory symptoms, they would be similar in adults and children: Xu et al.³ reporting 80% rectal swab positivity in some COVID-19 children

suggested that gastro-intestinal involvement would be more common among children.

The oral cavity has been identified as a vulnerable target too, with a prevalent ACE2 tongue expression (oral tongue, followed by floor of mouth and tongue base) rather than buccal/gingival tissues.¹

Salivary glands may act as a target, with ACE2 expression in the tongue even higher than that observed in different anatomic subsites within the aerodigestive tract,¹ suggesting that salivary glands may act as reservoir also in asymptomatic patients.⁴

Some authors^{5,6} documented ACE2/TMPRSS2 in nasal respiratory epithelial cells, olfactory epithelial support, and stem cells, but not in the olfactory sensory neurons, suggesting a non-neuronal expression within the olfactory epithelium that would serve as a virus reservoir responsible for both smell impairment and brain involvement.

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Different upper aerodigestive anatomic subsites are vulnerable targets for SARS-CoV-2 entry, active replication, and shedding, with transmission also possibly originating from patients complaining of less-quoted clinical manifestations (salivary gland infection).⁴

With regard to clinical manifestation, it has been largely reported that children less frequently develop both symptomatic and severe disease and have a very low estimated mortality rate compared to adults.⁷ As a fact, in Italy, one of the hardest-hit country in the world, only 1.2% of affected patients were children,⁷ and a recent metanalysis reported that 95% of pediatric cases present a clinical pattern of disease ranging from asymptomatic to mild/moderate disease.⁷

The peculiar pattern of disease in the pediatric age and the data about the prevalent expression of ACE2 on gastrointestinal host cells rather than in the respiratory system raise intriguing questions about the role (facilitating rather than exclusive?) of ACE2 for SARS-CoV-2 infection, the route of transmission, and the real burden of disease in children.

With regards to this age class, some considerations may be derived from the finding of contaminated *Mycoplasma* sequences from the cell line VeroE6/TMPRSS2 at next-generation sequencing analysis. This is consistent with previous findings documenting that simultaneous infection with *Mycoplasma* species would enhance cytopathic effect in VeroE6 cells persistently infected with SARS-CoV.⁸ This effect would be exerted by promoting apoptosis of surviving cells escaped from SARS-CoV-2-induced death, thus preventing the establishment of long-lasting infections. Given that airway colonization by *Mycoplasma* species is particularly frequent in pediatric age, with bacterial location within the pharynx and the mucosa-associated lymphoid tissue, it cannot be excluded that respiratory microbiota would modulate host susceptibility to SARS-CoV-2, possibly resulting in a reduced pathogenesis in children. The real action (immunologic/anatomic barrier? microbiota banking?) exerted by hypertrophic adenotonsillar tissue in determining clinical manifestations in children deserves further investigations.

A full understanding of SARS-CoV-2 tropism for human cells and more insights about cell type-specific expression of host cell receptors represent crucial steps to achieving a comprehensive knowledge of SARS-CoV-2 pathogenesis and transmission route. Molecular mapping would be desirable to test susceptibility to SARS-CoV-2 infection across specific anatomic subsites of the upper

aerodigestive tract, especially in the pediatric age, in order to drive clinical policies aimed at improving the diagnosis and limiting transmission.

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