EDITORIAL

Maternal immunity, a way to confer protection against enteropathogenic *Escherichia coli*☆,☆☆

Imunidade materna, uma forma de conferir proteção contra *Escherichia coli* enteropatogênica

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Diarrheal diseases caused by *Escherichia coli* remain as important causes of morbidity and mortality worldwide; children in the developing world suffer the major burden of diarrheal illnesses, while the burden among children and adults in the developed world is more evenly distributed.\(^1\) At least six different *E. coli* pathovars have been associated with diarrheal disease, and each one uses a distinct collection of virulence factors to subvert host cellular functions and potentiate their virulence, resulting in distinct clinical manifestations.\(^2,3\) One of the oldest and better characterized diarrheal pathovars is enteropathogenic *E. coli* (EPEC), which encompass a group of isolates that are a significant cause of persistent watery diarrhea among children worldwide.\(^4\) EPEC isolates belong to a limited number of O:H serotypes, and are known to carry the locus of entero-ocyte effacement (LEE), a region that encodes several proteins mediating the interaction with the host cells and the formation of a distinct lesion known as attaching and effacing (A/E).\(^2\) Moreover, EPEC strains may contain a virulence plasmid called EPEC adherence factor (EAF), because it encodes gene products involved in the synthesis and assembly of the bundle-forming type IV pilus (bfp), and also lacks the genes encoding for Shiga toxin (stx) production.\(^2\) The pEAF plasmid is used to sub-classify these strains into typical EPEC (tEPEC; those that are LEE+/stx+/bfp+) and atypical EPEC (aEPEC; those which are LEE+/stx−/bfp−).\(^5,6\)

In contrast, the related pathovar enterohemorrhagic *E. coli* (EHEC) possess the genotype LEE+/stx+/bfp−, and production of stx is associated with further systemic complications.\(^2\)

To this day, EPEC continues to be responsible for 5%–10% of pediatric diarrhea in developing countries; however, it is reported that the frequency of EPEC (particularly tEPEC) infections drops with age, and therefore adults rarely experience tEPEC episodes.\(^5,7\) Interestingly, infant acute diarrheal episodes caused by tEPEC have been declining throughout the years in many countries, including Latin America and Europe.\(^4,8\) Moreover, a large study conducted in several countries in Africa and Asia by the Global Enteric Multicenter Study (GEMS) network demonstrated that tEPEC strains were not among the leading pathogens causing acute moderate and severe diarrhea in these geographical regions.\(^8\) However, tEPEC infection appears to be associated with a 2.8-fold increased risk of death among infants aged 0–11 months.\(^9\) In contrast, aEPEC continues to be isolated...
in both developing and developed countries; in some
countries, they have surpassed EPEC infections.\textsuperscript{5,10} In some
studies from developing countries, it was demonstrated that
aEPEC isolates were responsible for 78% of all EPEC cases
in children aged less than 5 years.\textsuperscript{7} Regardless of whether
tEPEC or aEPEC are responsible for the diarrheal episodes or
the geographic distribution of the isolates, it is clearly evi-
dent that EPEC isolates are still among the most important
pathogens causing diarrhea.\textsuperscript{5,6,10} Thus, there is a need for a
therapeutic intervention to reduce the number of cases
worldwide.

Ideally, the most effective way to protect infants from
EPEC infection is by antibodies acquisition through active
or passive immunization. Several studies have strongly sug-
gested that breastfeeding might be able to protect infants
against EPEC due to the presence of antibodies directed to
specific EPEC virulence factors.\textsuperscript{11-15} There have been several
reports of antibodies against various secreted or surface-
located EPEC virulence factors, including those encoded on
the LEE pathogenicity island or the virulence pEAF plas-
mid, which can bind these factors and potentially block
bacterial colonization.\textsuperscript{2,3,11-15} From those immunogenic pro-
teins, a key virulence factor is intimin, the main EPEC
and EHEC membrane-located adhesin, which is encoded by
the eae gene within the LEE pathogenicity island.\textsuperscript{2} Several different types of intimins have been reported
based on the polymorphisms within their C-terminal region
(known as Inl280) and the most frequently found are the
\( \alpha \), \( \beta \), and \( \gamma \) types.\textsuperscript{2,15} The distribution of these intimin
proteins is associated with different EPEC and EHEC evo-
lutionary lineages. Intimin \( \alpha \) is found within the EPEC
lineage known as EPEC-1; intimin \( \beta \) is distributed among
human and animal pathogens, including EPEC2, EHEC-2,
and Citrobacter rodentium; whereas intimin \( \gamma \) is asso-
ciated with EHEC O157:H7 and aEPEC strains.\textsuperscript{8} It has
been previously shown that human immunoglobulins (e.g.,
secretory IgA) from breast milk can inhibit EPEC local-
ized adherence to cultured cells \textit{in vitro} and that these
immunoglobulins are also able to recognize different intimin
proteins.\textsuperscript{11-15}

Epidemiological studies in Brazil\textsuperscript{16} have elucidated
a quite unique map for the distribution of EPEC pathovars,
confirming the prevalence of these pathogenic E. coli iso-
lates and reinforcing the fact that aEPEC strains have
replaced tEPEC as the most prevalent EPEC subclass
associated with human disease in this country.\textsuperscript{17} Interes-
tingly, early acquisition of antibodies against intimin by
healthy Brazilian children living in endemic areas has been
demonstrated,\textsuperscript{14} suggesting that those antibodies might be
responsible for protection against the pathogen. Moreover,
it has been found that serum IgG and secretory IgA anti-
bodies are reactive against conserved and variable regions
of the intimins \( \alpha \), \( \beta \), and \( \gamma \); the cross-reactivity among
anti-intimin antibodies has also been demonstrated.\textsuperscript{15} These
studies suggest a correlation between the concentration of
the antibodies in both serum and colostrum and the proba-
bility protection elicited in children receiving these antibodies
via breastfeeding. Furthermore, the cross-reactivity of the
antibodies with different intimins suggests that it is possi-
bile to protect against different A/E-producing \textit{E. coli} (e.g.,
EPEC or EHEC).\textsuperscript{15}

In a recent study published in the Jornal de Pediatría, Alt-
man et al. investigated the transfer of maternal anti-intimin
antibodies from healthy Brazilian mothers to their newborns
through the placenta and colostrum, and found a variability
in the concentrations of these antibodies.\textsuperscript{18} The antibod-
ies displayed differential reactivity to different types of
intimins as well as to the different (conserved and variable)
regions of the intimins \( \alpha \), \( \beta \), and \( \gamma \). Interestingly, the inves-
tigators found that IgG serum antibodies, reactive to all the
intimin subtypes, were transferred to the newborns, and
that the antibody concentrations varied depending on the
structural region of the intimin protein tested (conserved vs.
variable).\textsuperscript{18} This study has significant implications for
the development of a potential treatment because in addi-
tion of demonstrating that anti-intimin antibodies can be
transferred from mothers to newborns through the placenta,
reinforcing the importance of passive immune protection
against pathogenic \textit{E. coli}, it opens the door for the develop-
ment of other immunization approaches to effectively
combat these pathogens.

Because EPEC and other A/E-producing \textit{E. coli} require
multiple virulence factors to cause disease, in addition to
the intimin protein, it might be feasible to propose the
development of a vaccine that targets multiple EPEC/EHEC
antigenic epitopes and which is administered to expect-
ing mothers. If maternal antibodies are generated against
different \textit{E. coli} antigens and can be transferred to new-
borns, then this type of vaccine should be the next priority
to combat pediatric diarrheal disease.\textsuperscript{19} In the past, EPEC
has also been the target for development of cattle immune
milk.\textsuperscript{19} Initial efforts using milk immunoglobulin concen-
trate containing antibodies to different EPEC strains, prepared
by hyper-immunization of pregnant cows, and used to treat
infants with gastroenteritis, resulted in over 80% of children
testing negative in their stools for different EPEC isolates.\textsuperscript{19}
This approach, as well as the study by Altman et al.,\textsuperscript{18}
provide evidence that treatment with specific antibodies
found in milk should be further explored as an effective way
to eliminate or prevent EPEC colonization of the intestine.

Conflicts of interest
The author declares no conflicts of interest.

References
1. Torres AG. \textit{Escherichia coli} in the Americas. Cham: Springer
International Publishing; 2016.
3. Kalita A, Hu J, Torres AG. Recent advances in adherence and
invasion of pathogenic \textit{Escherichia coli}. Curr Opin Infect Dis.
4. Hu J, Torres AG. Enteropathogenic \textit{Escherichia coli}: foe or inno-
5. Scallen KY, Fagundes-Neto U. Typical enteropathogenic
\textit{Escherichia coli}. In: Torres AG, editor. \textit{Escherichia coli in the
Americas}. Cham: Springer International Publishing; 2016. p.
59–76.
6. Gomes TA, Yamamoto D, Vieira MA, Hernandes RT. Atypi-
cal enteropathogenic \textit{Escherichia coli}. In: Torres AG, editor.
7. Scaletsky IC, Fagundes-Neto U. Typical enteropathogenic
\textit{Escherichia coli}. In: Torres AG, editor. \textit{Escherichia coli in the
Americas}. Cham: Springer International Publishing; 2016. p.
59–76.
8. Gomes TA, Yamamoto D, Vieira MA, Hernandes RT. Atypi-
cal enteropathogenic \textit{Escherichia coli}. In: Torres AG, editor.
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