COVID-19: risk of infection is high, independently of ABO blood group

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When a French aircraft carrier set sail on 22 January, 2020 for a mission of several months, its 1,769 crewmembers were unaware of a stowaway in the form of a novel virus. The SARS-CoV-2 virus, assumed in early 2020 to be a recent arrival in Europe, was already on board. Upon the ship’s return to Toulon, the main naval base of France on the Mediterranean Sea, most of the crew were confined to their barracks and 1,688 sailors participated in health monitoring. In this issue of Haematologica, Boudin and colleagues report data from this unique epidemiological setting,1 which could have hardly been better designed, if it had been set up for the purpose of studying a SARS-CoV-2 outbreak among young professionals.

After 1 month at sea, the first case of COVID-19 was recognized. Another month went by before an epidemic broke out, which forced the ship’s early return to base within 2 weeks. Several viral strains were detected by nucleotide sequencing.1 This observation could imply the embarkation of multiple sailors who were independently infected, an unlikely scenario in Europe so early in the pandemic. Possibly, only one crewmember was the source, and the initial strain evolved within the 12 weeks’ voyage while spreading among the crew.

Due to its exponential rate of spread, the SARS-CoV-2 virus rapidly infected at least 1,279 sailors, 76% of the participants of the study, whose median age was 28 years. Only 13% were female, without difference in the infection rate between males and females.1,2 This rate seemed strikingly high among young, healthy individuals,2 although it may not differ so much from that of other SARS-CoV-2 outbreaks, but rather reflected an exceptionally thorough follow-up and documentation. Only 14% of the infected participants remained asymptomatic.1 The median age of the 19 patients requiring only oxygen therapy was 45 years; the five patients admitted to intensive care units were older than 50 years. All infected sailors recovered eventually. These relatively benign clinical courses may not be representative of COVID-19 among the general population or cruise ship passengers, with a decidedly older age profile and related comorbidities.3

A PubMed search for “ABO in COVID-19” yielded more than 50 publications including reviews and meta-analyses,4 documenting this possible correlation as a topic of intense research in the past 9 months.3,6 The study by Boudin et al.1 provides data leading to an important clarification: the rate of infection among young adults is independent of ABO blood group. This study can be considered the definitive conclusion on this aspect, as the quality of the epidemiological data was optimal. Studies in smaller cohorts7-10 and less well-defined epidemiological settings7-9,11 should be considered with caution, even if there are many. They are more likely to be affected by unknown confounders. Particular precaution should be applied when COVID-19 was associated with ABO along with other blood group systems.10 Better data on ABO blood group and SARS-CoV-2 infection may not be accrued soon, and any future study would have to measure up to the quality of the study by Boudin et al.1 Can the ABO in COVID-19 topic be considered settled?2

An early study did not claim an influence of ABO on the SARS-CoV-2 infection rate.12 Rather the clinical course and disease outcome in patients, once infected, may differ depending on the ABO blood group.13,14,15 The lack of convincing evidence for an association between ABO and outcome in some11,14 even many, studies cannot be construed as convincing evidence for lack of such an association. The largest and most comprehensive data set so far was from patients with respiratory failure.15

This genome-wide association study15 reported a small association signal coinciding with the chromosomal position of the ABO blood group system. Outcome was better for patients with blood group O than for those with blood group A. The study design was criticized for using blood donors as the majority of controls.14 Using flawed control cohorts is a notorious cause of erroneous conclusions;16 and blood donors are generally selected in favor of blood group O.17 However, it remains to be explored whether the odds ratio introduced by this well-founded bias of Spanish16 and Italian donor recruitment, could entirely explain the odds ratio of excess death associated with blood group A.15 Even
a modest influence of ABO blood group on outcome should not be neglected, as happened once the SARS-CoV-1 epidemic abated, but should be investigated and resolved. Minor effects are important in precision medicine enabling comprehensive treatment of patients with COVID-19.

Less than 20% of patients with COVID-19 received blood transfusions. The details of ABO matching can easily be reported, as they are routinely known. When properly documented, the combined data from small prospective observational studies can amount to impressive case series. ABO data may offer surprising insights, as cellular blood components contain residual plasma, and often a lot. For logistical reasons, components that are not ABO-identical can be transfused in a “major ABO-compatible” way (for instance, O red cells to an A recipient), without explicitly informing the hematologists. In such cases, anti-A or anti-B from the donor will bind to cell surfaces of the recipient’s tissues and form immune complexes with A or B antigens that are soluble in the recipient’s plasma. This pathophysiology applies particularly to the transfusion of plasma components.

Convalescent plasma use in randomized clinical trials, in other clinical studies, and outside of them, is monitored for safety, best including ABO matching. Evidence is lacking to direct our practice on ABO matching of convalescent plasma. Hence, policies reflect the understanding and application of the basic principles of ABO compatibility, which have not been corroborated for COVID-19. “Minor ABO-compatible” plasma (for instance, AB plasma to an O recipient) transfers soluble A and B antigens. When bound by the recipient’s anti-A or anti-B, immune complexes are formed. These are a known trigger of the innate immune system, which receives another boost from the complement in the transfused plasma. Coagulation factors differ based on the patient’s ABO blood group and are, of course, also transfused by plasma. The interaction of complement and coagulation is not well understood in critically ill patients with COVID-19, whose potential harm from convalescent plasma should be considered and limited.

Convalescent plasma, containing high-titer anti-SARS-CoV-2 and neutralizing antibody, can be tested for isoagglutinin titers, too. Convalescent plasma with high-titer anti-A or anti-B should be transfused to ABO-identical recipients, and a low-titer product is best for immune globulin manufacturing. Any indication to transfuse blood components containing plasma, particularly if not ABO identical, should be carefully considered and the exposure evaluated in studies. The ABO blood group system may have some influence on disease progression, once an individual is infected by SARS-CoV-2 and falls ill. The study by Boudin et al. in its unique epidemiological setting offered convincing evidence that becoming infected with the virus was not influenced by the ABO blood group in young professionals. This difference is not surprising, as the mechanisms involved likely differ between infection and disease progression.

The sailors’ experience in spring 2020 should serve as a reminder: the risk of acquiring a SARS-CoV-2 infection is exceptionally high among young adults exposed to the virus in certain circumstances and no ABO blood group type can protect an individual from becoming infected.

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## Expanding dasatinib beyond KIT in acute myeloid leukemia

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The goal of personalized medicine is to match patient-specific factors with relevant therapeutic options. The therapeutic conundrum in acute myeloid leukemia (AML) remains the heterogeneity of the disease and the paucity of treatment options for which there are highly predictive biomarkers. AML is broadly heterogeneous across all measured axes, including morphological presentation, cytogenetics, point mutations, expression signatures, epigenetic signatures, and chromatin signatures.\(^1\)\(^2\) Furthermore, within patients, subclonal architecture suggests ongoing acquisition of new variants and expression signatures,\(^3\) providing for intrapatient leukemic heterogeneity as well as interpatient heterogeneity. Just as heterogeneity can be seen across a range of measurements, response diversity has been mapped to clinical and molecular diversity, providing prognostic opportunities, but not yet personalized opportunities.\(^4\)

AML results in unrestrained growth of the leukemia cells *in vivo*, but this has not translated into easy *in vitro* growth sufficient for effective cell manipulation in laboratory settings. Primary human AML cells grow poorly in liquid tissue culture media or methylcellulose. Only a fraction of samples will effectively engraft into immunodeficient mice, and among these, it is often only a subclone that engrafts.\(^5\) Recent progress has made short-term *ex vivo* culture possible, and improvements in the immunodeficient hosts have improved xenograft potential.\(^6\)

*Ex vivo* analysis of chemotherapy has been championed by several groups, including the large-scale BEAT AML project.\(^6\) Studies have increasingly suggested *ex vivo* correlations with clinical response and the feasibility of scaling up to achieve sufficient throughput to identify useful functional biomarkers of sensitivity and resistance to chemotherapy.

In this issue, Tavor *et al.* present a focused analysis that leverages careful sample selection with *ex vivo* drug sensitivity.\(^7\) They applied a 384-well approach to interrogate cell viability in liquid culture after 48 hours assessed across 46 drugs, each at 12 concentrations, which provided a broad area under the curve (AUC) measurement. In this assay, the authors used cytokine combinations (colony-stimulating factor, interleukin 3, interleukin 6, thrombopoietin) in liquid culture and avoided stromal cell co-culture to facilitate viability read-out using a streamlined ATP-dependant assay (Cell Titer Glo). This approach provides an efficient read-out of early chemotoxicity, but does not provide an effective measure of differentiation or the cell toxicity that occurs after several days of exposure or cell divisions. In evaluating outcomes using this design, it is worth noting that the strong cytokine stimuli in the tissue culture may bias cell survival and chemosensitivity to cells that are capable of utilizing those signaling pathways or dependent on their stimuli for survival, and the small cell numbers evaluated in 384-well formats focus outcomes on phenotypes in the bulk cell population.

Tavor *et al.* found that relapse samples were less chemosensitive than the paired diagnostic sample, across diverse classes of chemotherapy. Indeed, there were statistical differences between the sensitivity of diagnostic and relapse pairs to some common salvage agents, including...