Minimizing the Risk of Xenozoonosis

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Microbiological quality control of pigs to be used as sources of organs for xenotransplantation will require a new approach to the care of pigs. Assessment of the potential risk associated with pig-to-human transplantation and steps to minimize this risk have been considered by an Advisory Board set up by Novartis Pharma and reported by Onions et al.[1] In the present paper, general concepts for minimizing the risk of xenozoonosis from pigs will be described, based on the deliberations of the above Board, with special emphasis on the importance of viruses (with the exception of porcine endogenous retroviruses (PERV), which are discussed elsewhere in this issue).

Microbiological Quality Control of Organ-Source Pigs

Issues relating to the potential risk provided by zoonotic agents have been of concern in the development and production of vaccines for human use, as most of these are prepared in animals or in animal cell culture. Assay systems to ensure exclusion of adventitious microorganisms in such vaccines are now well-established. Pig organs for xenotransplantation can be considered essentially as biologic products, similar to these vaccines. However, the transplantation of a pig organ into a heavily immunosuppressed human recipient may pose an unprecedented risk significantly different from that posed by a vaccine. Moreover, it is difficult to test the final product, i.e., the organ to be transplanted, to ensure exclusion of all microbiological agents of concern. This difficulty can be overcome to a large extent by isolating cohorts of organ-source pigs, enabling extensive microbiological testing to be made on the cohorts and, particularly, on sentinel animals that represent the entire group.

The founder pigs should be obtained by hysterectomy or hysterotomy from sows from an established specific pathogen-free herd. These offspring will be free of most microorganisms, with the exception of those transmitted in utero and those that are integrated into the chromosomes, such as PERV. These piglets can be raised in an isolator with positive pressure for the first 2-8 weeks, which period of time is acceptable from the perspective of animal welfare. Thereafter, they can be maintained in a biosecurity barrier, and the subsequent breeding herd may be established by natural delivery. Actual organ-source pigs may be derived either by hysterotomy or by natural delivery followed by segregated early weaning.[2]

It will be essential for the organ-source pigs to be housed and maintained in a biosecurity barrier building, which is equipped with HEPA filters for air filtration and where the air pressure is kept positive. Special attention should be paid to prevent the entry of insects into the building, such as mosquitoes and ticks, as many arthropod-borne viruses are known to infect pigs. Monitoring the health of the human staff will be important in order to exclude those with infections from the building: a rigorous occupational surveillance program will therefore need to be established. Mammalian and fish proteins, except milk-derived lactose, should be eliminated from the pig feed to prevent infection with prions. All the feed should be sterilized, and drinking water should also be sterilized by ultrafiltration. Use of vaccines for viruses and bacteria should be avoided as they may mask early clinical signs of infection and/or interfere with serological monitoring of the herd.

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Risk of Bacteria and Fungi

The risks associated with bacteria as xenozoonotic agents are considered to be less than those of viruses. Nevertheless, all pathogenic bacteria that cause systemic disease in pigs, or affect any of the organs used for transplantation, should be excluded. The exclusion of multi-drug resistant bacteria is especially important. Fungi are usually acquired from the external environment, and are not considered to pose a particular risk, except for systemic mycosis.

Risk of Viruses

Viruses pose special risks. In view of the potential for cross-species infection by viruses, not only swine-specific viruses but also other viruses that could possibly infect pigs need to be rigorously excluded. Most of viruses that cause disease in pigs are satisfactorily controlled in the pig industry. However, some viruses that are transmitted vertically, such as porcine circovirus and porcine cytomegalovirus, will be difficult to eliminate if they infect the breeding herd.

Pigs harbor several zoonotic viruses that cause disease in humans. Some of them are geographically restricted to certain regions. For instance, equine encephalitis viruses are endemic in the American continent, but not in Asia and Australia. On the other hand, Japanese encephalitis virus is endemic in Asia and Australia, but not in the American continent or Europe. Therefore, testing protocols will require special consideration depending on both the type of virus and the geography being considered. However, it should be borne in mind that "globalization" may change the geographic distribution of a virus, as illustrated by the recent introduction of West Nile virus into New York.

Risk of Prion

Animal prion diseases occur solely as infectious forms, there being no evidence of sporadic or genetic types of these diseases. Therefore, a vegetarian diet will prevent the transmission of prion disease. Moreover, the susceptibility of pigs to bovine spongiform encephalopathy has been shown to be remarkably lower than that for sheep or goats. Thus, the potential risk of prion disease in the organ-source herd is considered to be extremely remote.

Risk of Unknown Viruses

Newly-emerging (hitherto undocumented) viruses are of some concern as several have been found to infect pigs. These include porcine hepatitis E virus, Menangle virus, porcine lymphotropic herpesvirus, and Nipah virus. With increased awareness, partly as a result of increasing interest in xenotransplantation, hitherto unknown viruses that infect pigs will continue to be identified. However, it is extremely unlikely that these will be a hazard to pigs housed under the isolated conditions outlined above.

Archiving of Tissues

Comprehensive archiving of the tissues from both the organ-source pigs and the human recipients of pig organs or tissues will need to be established. Detailed records of the health history of both pigs and patients will also be essential. In the event of an infection in the recipient, records and tissue from the organ-source pig will be available for study to elucidate the cause and nature of the infection and, in particular, to determine whether it is the result of xenozoonotic transmission.

References

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