



Does gallium-citrate have yet another story to tell? Lessons relevant to the COVID-19 era

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The evolution of [⁶⁷Ga]Ga-citrate as an imaging agent over the past three quarters of a century is fascinating from a historical point of view [1, 2]. Its storied saga recalls the formative years in the rise of nuclear medicine and many of the important diagnostic roles that scintigraphy played in the provision of health care over the past seven decades. [⁶⁷Ga]Ga-citrate was introduced at the time when mechanisms of localization of radiopharmaceuticals were rather opaque and choice of radiopharmaceuticals often proceeded by trial and error, if not by outright serendipity. Raymond Hayes has succinctly summarized this odyssey from a first-hand perspective [1]. In the late 1940s, non-radioactive gallium metal was being considered as a coolant for use in nuclear powered naval vessels which stimulated studies on the metal's biodistribution. Utilizing the tracer principle, Dudley and coworkers determined that [⁷²Ga]Ga-citrate (and ionic gallium, in general) localized to a large degree at sites of osteogenesis [3, 4]; based on these findings, in the pre-technetium imaging agent era, there was interest in developing the radiopharmaceutical into a bone imaging, and potentially therapeutic, modality [5]. Gallium-72's decay properties were eventually deemed insufficiently favorable for human use. Investigators at Oak Ridge and Bethesda subsequently turned their attention to [⁶⁷Ga]Ga-citrate, with its improved decay properties, but were chagrined to observe that the citrate ion of this radioisotope did not replicate the biodistribution seen with [⁷²Ga]Ga-citrate; they quickly realized that the disparity arose because of variation in specific (molar) activity of the radiopharmaceutical [6, 7]. Gallium-72, derived from reactor-production, contained

chemically significant amounts of non-radioactive ("carrier") gallium, while Gallium-67 was produced in a cyclotron and was "carrier free", that is without addition of non-radioactive gallium atoms. Both radioisotopic forms of gallium-citrate were deemed not useful for bone imaging and were shelved for a decade. In the 1960s, investigators at Oak Ridge rekindled their interest in gallium as a means of bone imaging (including the possibility of addition of carrier gallium as needed), in part stimulated by new availability of Gallium-68. According to Hayes [1], the investigators were amazed to observe that carrier-free [⁶⁷Ga]Ga-citrate intensely localized in lymph nodes of a patient with Hodgkin's disease [8], thereby laying the ground-work for what would subsequently become extensive use of carrier-free [⁶⁷Ga]Ga-citrate for clinical tumor imaging [9]. It was understood that ionic gallium in the blood was bound to circulating transferrin much in the way that iron is bound. Reliance on gallium scanning for lymphoma staging would prevail for decades, only waning in the 2000s when eclipsed by the novel radiopharmaceutical (D)-2-[¹⁸F]Fluoro-deoxy-glucose ([¹⁸F]FDG), coupled with widespread availability of PET-CT cameras [10].

Another twist in the circuitous story of gallium emerged in the early 1970s, when it was serendipitously noted that [⁶⁷Ga]Ga-citrate was not specific to tumor but also localized in sites of inflammation and infection [11–13]. The indefatigable radiopharmaceutical therefore emerged as a useful agent for infection imaging. Availability of this technique dovetailed with a surge in infectious disease coincident with emergence of the AIDS epidemic in the 1980s, which unfortunately presented much opportunity for imaging of previously rare and unusual infections such as atypical tuberculosis, and *Pneumocystis jiroveci*. [⁶⁷Ga]Ga-citrate was noted to be an effective means of imaging in virtually all of the AIDS-related tumors and infections, with the exception of Kaposi's sarcoma, where [²⁰¹Tl]Thallium-chloride held sway [14]. While ¹¹¹In-labeled white blood cells were also effective in imaging suppurative infections, one of the advantages of gallium in these populations was that it did not require handling

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of blood products, and imaging could be performed in patients with leukopenia [15].

One is struck when reviewing the early gallium literature on the disparity between the widespread adoption of the radiopharmaceutical and the corresponding paucity of insight into its mechanisms of action. A qualitative leap in the understanding of [^{67}Ga]Ga-citrate came when Dr. Steven Larson conceptualized the gallium-transferrin conjugate as a ligand that binds to a tumor-associated transferrin receptor [16]. This understanding helps to explain the crucial importance of specific activity; when cold gallium is present, it competes to displace the labeled substrate from the transferrin receptor, thereby markedly changing the biodistribution. In much the same way, the transferrin hypothesis explains the curious relationship of [^{67}Ga]Ga-citrate imaging and conditions causing iron overload, such as multiple transfusions, which also result in altered biodistribution [17]. Here too, the iron excess displaces gallium ions from the critical transferrin molecule, thereby decoupling the transferrin ligand from the radionuclide, which now behaves as an independent moiety. With respect to mechanism of uptake in infection, several possibilities have been postulated. These include regional hyperemia, increased vascular permeability and an expanded extracellular space, and the presence of gallium-avid proteins in the inflammatory exudate. Other implicated factors are the binding of gallium species in solution to leukocytes, bacteria, and their respective breakdown components of lactoferrin and siderophores [18, 19].

As an imaging radiopharmaceutical, [^{67}Ga]Ga-citrate is hampered by several objective limitations including non-ideal dosimetry, a prolonged delay between administration and imaging, suboptimal image quality, and a lack of specificity [20]. Nonetheless, [^{67}Ga]Ga-citrate is still useful in a subgroup of cases of infection and inflammation, especially where [^{18}F]FDG is not an option due to lack of availability or reimbursement. The Image of the Month by Zamora et al. [21] features an elderly woman who presented with evolving COVID-19-related lung infiltrates and presumed mastoiditis. Gallium scintigraphy was performed for the purpose of evaluating infection at the skull base. There was increased [^{67}Ga]Ga-citrate uptake in the right mastoid, confirming active infection. In contrast, the confluent COVID-19-related parenchymal lung densities, which were included on the whole-body images and on the SPECT-CT field-of-view, did not take up more than minimal amounts of radiopharmaceutical. An additional tantalizing aspect of this case is the discrepancy between the minimal [^{67}Ga]Ga-citrate uptake that we describe in the characteristic extensive lung infiltrates, and relatively intense [^{18}F]FDG uptake which has been described in similar patients in a number of case reports [22–24]. A second patient with typical, though less extensive COVID-19-related lung infiltrates, has also come to our attention and did not demonstrate significant gallium uptake, confirming our initial observation.

Large gaps exist in our understanding of the pathophysiology of COVID-19-related lung disease [25]. The disparity between reported [^{18}F]FDG uptake and the lack of [^{67}Ga]Ga-citrate uptake that we observed in COVID-19-related parenchymal lung densities certainly represents an enigma and may present medical researchers with some clues as to the nature of COVID-19 lung pathology. Mechanisms of [^{18}F]FDG uptake are well understood and imply active transport of radiopharmaceutical via glucose transporters chiefly GLUT1 and GLUT3, as well as phosphorylation by hexokinase. These features are all prevalent in cells involved in infection and inflammation, especially neutrophils and the monocyte and macrophage family [26, 27]. [^{67}Ga]Ga-citrate uptake in inflammatory and infectious processes has been tied to several putative mechanisms we have discussed earlier, though the relative importance of each does not appear to be well-understood. The minimal uptake, observed in these two patients, does suggest absence of iron-binding receptors in the cellular response, which is hard to fathom because the same neutrophils and macrophages implicated in [^{18}F]FDG uptake should be associated with gallium citrate binding. Post-mortem lung tissue obtained from patients infected with COVID-19 has shown damage to the lungs consistent with ARDS, focal necrosis, and lymphocytic and monocytic infiltration [28]. An intriguing though speculative theory to explain the paucity of [^{67}Ga]Ga-citrate uptake is that the profound perturbations in iron-binding proteins associated with serious COVID-19 disease, evidenced by the markedly increased ferritin levels [29], may somehow interfere with the binding and metabolism of [^{67}Ga]Ga-citrate. It is conceivable that the uptake at the site of mastoiditis may at least in part represent enhanced “bone tracer” effect of gallium ion when displaced from the transferrin molecule.

There is much to be learned from gallium’s circuitous narrative, including the importance of serendipity in radiopharmaceutical development, the ability to think out-of-the-box and be receptive to trajectories that were not initially envisioned, and from a basic science point of view, the importance of specific activity on radiopharmaceutical biodistribution and the idea that the fate of a radiolabel may not always represent the behavior of the ligand. Lessons learned in the past will no doubt be relevant to applications in the future. It is interesting to speculate as to what chapters are yet to be written in the saga of gallium isotopes. Gallium-68, as the radiolabel of various somatostatin analogs, has made a great impact on the imaging of neuroendocrine tumors [30] and is being evaluated for labeling of PSMA-targeting compounds in the imaging of prostate cancer [31]. [^{68}Ga]Ga-citrate has been developed as a substrate for PET-CT imaging in order to improve upon some of the limitations encountered when imaging [^{67}Ga]Ga-citrate [32, 33]. It is tempting to consider whether gallium radionuclides might possibly shed light on mechanisms of COVID-19-related lung disease or may somehow have useful application in the clinical evaluation of COVID-19 infection.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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