Radiotracers in Infection Imaging

Subjects: Radiology, Nuclear Medicine & Medical Imaging

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Several developments in the molecular imaging of infections target microorganism-specific metabolism and activity. By targeting substances that are presented by or released from the pathogenic microorganism or microorganism-specific metabolic pathways, more radiotracers can be developed whose localization mechanism is independent of the host immune response.

Radiolabeled antibiotics | Infection Imaging | diabetic foot infections

1. Introduction

Radiolabeled antibiotics are relatively well-studied in the context of imaging diabetic foot infection (DFI). Previously studied radiolabeled antibiotics target crucial features required for bacterial pathogenicity and survival, including the synthesis of folic acid required for nucleic acid synthesis, cell wall construction, cell membrane structure and function, transcription, and translation [1]. Antibiotic-resistant bacteria pose a major problem for radiolabeled antibiotics. Depending on the uptake mechanism, some bacteria may demonstrate radiotracer accumulation, while others may not. ^{99m}Tc-ciprofloxacin is a well-studied antibiotic imaging agent and, although previous studies originally demonstrated its high specificity, subsequent studies have not been able to reproduce the result [2][3][4][5]. *In vivo* studies of its ability to differentiate gram-positive from gram-negative bacteria have reached contradictory conclusions. The main drawback to ^{99m}Tc-ciprofloxacin is its accumulation in dead bacteria [2], which leads to false positives, as suggested by a large multicenter clinical trial that reported a sensitivity of 66.7%, a specificity of 85.7%, and an accuracy of 72% for both soft tissue infection and OM [6]. Several radiolabeled antibiotics have been studied to date (**Table 1**); however, the least well-studied are bacterial cell wall synthesis inhibitors such as vancomycin. The SPECT tracer ^{99} Tc-vancomycin, which was directly labeled, has demonstrated an affinity for *S. aureus* infectious foci. ^{99m}Tc-vancomycin labeled through ^{99m}Tc-Tc-HYNIC tetrazine click chemistry corroborated this observation with a three-fold uptake increase in a *S. aureus* infection site compared to controls [7]. Studies using fluorescently labeled vancomycin have also reported promising results [8], although isotopic-labeled vancomycin has shown greater uptake [9]. Although the ^{99m}Tc-vancomycin single-photon emission computed tomography (SPECT) tracer may have a valuable place in the clinical management of DFI, the development of a vancomycin PET tracer may provide better image resolution.

Table 1. Emerging Investigational Radiotracers of Infection Imaging.

	Radiotracer	Clinical Trials	Parameter	Mechanism of Localization	Strength/Weakness	References
Radiolabeled Antibiotics	^{99m}Tc-ciprofloxacin	Yes	Inhibition of DNA Synthesis	Bacterial DNA gyrase	High sensitivity (85.4–97.2%), ciprofloxacin already used in DFI treatment	[3][4][5][6]
					Low specificity (66.7–81.7%), antibiotic resistant bacteria	
	^{18}F-fluoropropyl-trimethoprim	No	Inhibition of Folic Acid Synthesis	Inhibition of thymidine biosynthesis	Low background, high uptake in bacteria, detect inflammation from soft tissue infection vs sterile inflammation	[10]
					Antibiotic resistant bacteria	
	^{99m}Tc-sulfonamides (pertechnetate, sulfadiazine)	No	Inhibition of Folic Acid Synthesis		Broad spectrum antibiotics, uptake in bacterial and fungal infections	[11]
					Antibiotic resistant bacteria	
	^{99m}Tc-vancomycin	No	Inhibition of bacterial cell wall synthesis	Binds to D-ala-D-ala lipid moiety	Specific for gram positive organisms	[7][8][9]
					Not specific for gram negative organisms Antibiotic resistant bacteria	
Radiolabeled Sugars	^{18}F-FDS	Yes	Bacteria-Specific Glucose Sources for Carbohydrate Metabolism	Bacterial Metabolic Substrate	Antibiotic treatment monitoring, used in humans	[12][13]
					Uptake by Enterobacteriaceae in the human gut	
	^{18}F-FAG	No		Sorbitol analogue	Selective accumulation in E.	[14]

	Radiotracer	Clinical Trials	Parameter	Mechanism of Localization	Strength/Weakness	References
				utilized only by bacteria	coli, rapid accumulation, can differentiate infection from sterile inflammation, shows promise for monitoring response to treatment, small molecule	
					Not applied clinically	
	^{18}F-maltohexose	No		Bacterial-specific maltodextrin transporter	Can discriminate between live bacteria, metabolically inactive bacteria, and sterile inflammation	[15]
					Poor signal-to-noise ratios, Not applied clinically	
	6″-^{18}F-fluoromaltotriose	No		Bacterial-specific maltodextrin transporter	2nd Gen, improved signal-to-noise ratio, bacterial-selective uptake in vitro and in vivo	[16][17]
					Not applied clinically	
	D-[methyl-^{11}C] methionine	No		Incorporation into the peptidoglycan	Distinguish sterile inflammation from infection in both gram—and gram +, broad sensitivity	[18][19]
Amino Acid Uptake			Bacterial Cell Wall Synthesis		Not applied clinically	
	D-5-[^{11}C] glutamine	No		Incorporation into the peptidoglycan	Highly specific, high sensitivity for gram +, no uptake in sterile inflammation, fast clearance	[20]
					Corroborating studies needed, not yet applied clinically	

	Radiotracer	Clinical Trials	Parameter	Mechanism of Localization	Strength/Weakness	References
Vitamin Uptake	^{124}I-fialuridine (FIAU)	Yes	Endogenous TK enzyme of pathogenic bacteria	Trapped in the cell after phosphorylation	Reduced uptake in the presence of metal artifacts, More clinical studies needed to assess clinical efficacy	[21][22][23]
	^{111}In-biotin	No	Production of Fatty Acid	Bacterial growth factor	Essential growth factor for S. aureus Corroborating in vivo studies needed to assess clinical relevance	[24]
	^{99m}Tc-PAMA	No	Vitamin B12 Metabolism	Vitamin B12 derivative that accumulates in rapidly proliferating cells	High uptake in Gram + and Gram - Not applied clinically	[25]
	^{18}F or ^{3}H-PABA	No	Folic Acid Synthesis	Inhibition of Thymidine Synthesis	Accumulation in MRSA and other resistant organisms In vivo studies needed	[26]
Polyclonal Antibodies	^{64}Cu-NODAGA	No	Membrane protein binding of polyclonal antibody	Microbe-specific membrane polyclonal antibody binding	Particular to a specific microbe Slow accumulation time	[27][28]
Siderophores	^{68}Ga-FOXE	No	Iron Transport	Accumulation of Siderophores in the cell	High uptake in S. aureus and fungi Not used in DFI model	[29][30][31]
Immunoscintigraphy	^{99m}Tc-sulesomab	Yes	WBC migration to infectious foci	Binds to antigen-90 on WBC membranes	Ease of preparation? Not sure about this Dependent upon host response,	[32][33]

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based imaging shows specificity, widespread adoption for clinical use may be limited because of the 20-min half-life of ^{11}C.

Microorganisms may also be targeted based on their vitamin uptake. Since biotin is used in the production of fatty acids and is an essential growth factor for *S. aureus* and other bacteria, it has been explored for infection imaging. Although little data are currently available, an *in vitro* study using [^{111}In]-In-DTPA-biotin reported selective uptake in *S. aureus* cultures [24]. In addition to targeting biotin, a radiolabeled vitamin B12 derivative, ^{99m}Tc-PAMA has also

Radiotracer	Clinical Trials	Parameter	Mechanism of Localization	Strength/Weakness	References
				[25] expensive, limited availability	
3A to synthesize			ng ^{3}H-PABA rep		in MRSA as well as
^{18}		[26]	Binds to antigen-95 on granulocytes and their precursors	Ease of preparation, good sensitivity and specificity	[32]
^{99m}Tc-Besilesomab				Dependent upon host response, expensive, limited availability	
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joint infections [34], a more recent study found that tracer uptake was reduced in the presence of metal artifacts [35]. A clinical study of 16 patients with suspected musculoskeletal infection, who underwent ^{18}F-FDG and ^{124}I-FIAU PET/CT, reported a range of specificity of 51.7–72.7% and a maximum sensitivity of 100%; however, the approach lacked specificity. The authors were also unable to perform a definitive cross-comparison of its diagnostic efficacy because of equivocal clinical findings in a large number of patients [21]. Aptamers are oligonucleotides that have been used to target the peptidoglycan cell wall. One group that used ^{99m}Tc-Antibac demonstrated its ability to distinguish between bacterial and fungal infections *in vivo* [11].

Siderophores are small molecules with a high affinity for Fe(III) and are produced primarily by bacteria but are also produced by virtually all microorganisms, including prokaryotes and eukaryotes [36]. Mammalian macrophages have been reported [13] as sources of siderophores [37]. Organisms use these metal-seeking molecules for extra- or intra-cellular metal transport and storage. Biological processes such as DNA replication, transcription, oxidative stress responses, and respiration all require transition metals. Iron and zinc are among the most abundant in living organisms. Iron is an essential cofactor for respiration and central metabolism. Zinc is the catalytic center for many enzymes and is required for 5–6% of all protein functions [38]. Siderophores are often categorized into the following groups, according to the chemical moiety that binds iron: catecholates, hydroxamates, and carboxylates. Mixed type siderophores have two or more of these moieties. Siderophores may actively alter their affinity for iron in order to bind other metals by increasing their expression of metal transporters [38]. Desferricoprogen—a natural siderophore produced by *Penicillium chrysogenum* and *Neurospora crassa*—reportedly bound to both trivalent (Al(III) and In(III)) or divalent (Cu(II), Ni(II), Zn(II), and Fe(II) metal ions [39]. Transport systems and siderophore production are unregulated during infection and can accumulate in bacteria as well as fungi. An *in vitro* study which used ^{68}Ga-ferrioxamine (^{68}Ga-FOXE) showed high uptake in *S. aureus*; however, it was not corroborated *in vivo* [29]. In fungi, *Aspergillus fumigatus*-specific fluorescent siderophore conjugates were used to assess pulmonary aspergillosis *in vitro* [30]; however, recent in vivo studies have only been performed to assess biodistribution in pulmonary aspergillosis [31]. Further research regarding specificity, sensitivity, and use in additional infection models is needed.

2. Immunoscintigraphy

In addition to *in vitro* labeling, WBCs may also be localized *in vivo* by using radiolabeled antibodies which target WBC antigens—a technique called immunoscintigraphy. For example, ^{99m}Tc-besilesomab uses the monoclonal

antibody besilesomab to bind to the granulocyte-specific antigen-95. Antigen-95 is present on the membranes of granulocytes and their precursors. Within 45 min of initial injection, 10% of the ^{99m}Tc-besilesomab is bound to neutrophils, while 20% is unbound but localizes to the site of infection by nonspecific mechanisms [40]. A recent study of 119 patients with suspected OM compared planar ^{99m}Tc-HMPAO WBC and ^{99m}Tc-besilesomab imaging in the diagnosis of peripheral OM. They found that ^{99m}Tc-HMPAO had a lower sensitivity than ^{99m}Tc-besilesomab (59.0% and 74.8%, respectively); however, ^{99m}Tc-HMPAO had a higher specificity than ^{99m}Tc-besilesomab (79.5% and 71.8%, respectively) [32]. ^{99m}Tc-sulesomab also binds to an antigen found on leukocyte membranes—antigen-90—but only 3–6% of ^{99m}Tc-sulesomab is bound to circulating neutrophils, and 35% is found in bone marrow 24 h post-injection [41]. The results of a study of combat-related infections suggest that ^{99m}Tc-sulesomab may not possess sufficient accuracy (78% accuracy) for the identification of the foci of infections but may have otherwise comparable diagnostic values (93% PPV, 62% NPV, 72% sensitivity, 88% specificity) [33]. One study of *Yersinia enterocolitica* infections used immunoPET with ^{64}Cu-NODAGA-labeled *Yersinia*-specific polyclonal antibodies to target the membrane protein YadA and reported colocalization in a dose-dependent manner with bacterial lesions in a murine model [27]. Another study that used the [^{64}Cu]NODAGA-IgG$_3$ monoclonal antibody from mice to examine *C. albicans* infections demonstrated its accuracy in diagnosing infection in vitro as well as in vivo [28]. A meta-analysis found a sensitivity of 81% and specificity of 86% for anti-granulocyte scintigraphy with monoclonal antibodies [42]. The use of intact antibodies takes up to several days to accumulate near infectious foci. Clinically, this could be a limitation because of the need for rapid identification of the infection site. However, the use of antibody fragments may lead to faster accumulation time. Overall, it appears that radiolabeled antibodies do not have the ability to replace existing methods in a clinical setting because of the relatively low diagnostic values reported by the studies discussed above.

One recent therapeutic application of US used in DFI is cavitation, in which ultrasonic waves are used to create microbubbles which form from the dissolved gas that accumulates in the wound. The molecular purpose of this treatment is to induce compression and movement of the wound cells and small ions to increase protein synthesis and the permeability of vascular walls and cell membranes [3]. Ultimately, reduced inflammation, angiogenesis, and increased cell proliferation and recruitment are expected at the site of infection [4]. Currently, only three studies have used this technique and two of them demonstrated either complete wound closure or a significant reduction in wound area [5][6][7].

3. Conclusion

Although these emerging imaging probes are targeting the microorganism rather than the host response, the quantitative measures of probe retention are generally much lower than the clinically available tracers that target the host response. Further, while most of these have not been used in DFI specifically, this is an opportunity for the expansion of molecular imaging approaches to DFI.

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