



Advanced imaging tools for childhood tuberculosis: potential applications and research needs

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Tuberculosis is the leading cause of death globally that is due to a single pathogen, and up to a fifth of patients with tuberculosis in high-incidence countries are children younger than 16 years. Unfortunately, the diagnosis of childhood tuberculosis is challenging because the disease is often paucibacillary and it is difficult to obtain suitable specimens, causing poor sensitivity of currently available pathogen-based tests. Chest radiography is important for diagnostic evaluations because it detects abnormalities consistent with childhood tuberculosis, but several limitations exist in the interpretation of such results. Therefore, other imaging methods need to be systematically evaluated in children with tuberculosis, although current data suggest that when available, cross-sectional imaging, such as CT, should be considered in the diagnostic evaluation for tuberculosis in a symptomatic child. Additionally, much of the understanding of childhood tuberculosis stems from clinical specimens that might not accurately represent the lesional biology at infection sites. By providing non-invasive measures of lesional biology, advanced imaging tools could enhance the understanding of basic biology and improve on the poor sensitivity of current pathogen detection systems. Finally, there are key knowledge gaps regarding the use of imaging tools for childhood tuberculosis that we outlined in this Personal View, in conjunction with a proposed roadmap for future research.

Introduction

Children constitute up to a fifth of patients with tuberculosis in high-incidence countries and account for 8–20% of tuberculosis-related deaths in high-incidence countries.^{1–4} Challenges in tuberculosis diagnosis and, consequently, the timely initiation of treatment lead to poor outcomes and can often have fatal consequences for young children. Children with tuberculosis tend to have a relatively low bacterial burden (paucibacillary disease), which makes detecting the organism difficult, even in patients with advanced disease. This paucibacillary nature of childhood tuberculosis leads to poor sensitivities (10–30%) of currently available pathogen-based tests, including nucleic acid amplification or microbiological culture assays.^{5,6} This limitation is compounded by the challenge of collecting respiratory specimens from young children suspected of having pulmonary tuberculosis who are unable to expectorate sputum, whether spontaneous or induced. Children have higher incidence of extrapulmonary tuberculosis than in adults⁷ and the diagnostic challenges of specimen collection and pathogen detection for childhood cases are greater. Symptom-based diagnostic approaches are suboptimal in young children and have even less diagnostic value in children living with HIV.⁸ Currently available tuberculosis immune-based tests—eg, the tuberculin skin test and blood test (T-SPOT, Oxford Immunotec, USA; and QuantiFERON-TB, QIAGEN, USA)—do not distinguish between infection and disease or past versus present disease, and a negative test does not rule out tuberculosis.⁹

In the absence of positive pathogen-based tests—ie, culture or nucleic acid amplification tests such as Xpert MTB/RIF (Cepheid, USA)—most cases of childhood tuberculosis are diagnosed on the basis of findings

suggestive of tuberculosis disease (eg, clinical signs and symptoms, radiological or medical imaging, laboratory and histopathological findings), or findings supportive of tuberculosis as the cause (eg, exposure history, immune-based tests, biomarkers for systemic inflammation, cell counts, biochemistry), and exclusion of alternative diagnoses. Access to imaging is insufficient in many low-resource settings, although chest radiography is often used in the diagnostic evaluation as complementary evidence of tuberculosis. However, there are limitations in

Key points

- Chest radiography continues to be a useful imaging modality for the initial radiological evaluation of children with suspected intrathoracic tuberculosis. To distinguish tuberculosis from other pathologies, chest radiography interpretation should be limited to findings such as the detection of the Ghon complex, miliary nodules, and airway compression, and it is important to recognise its limitations.
- Currently available imaging modalities, such as ultrasound and cross-sectional imaging, can improve the diagnostic accuracy of intrathoracic tuberculosis. When available, cross-sectional imaging such as CT, should be considered in the diagnostic evaluation for tuberculosis in a symptomatic child.
- Educating the public and clinicians about the risks and benefits of using available imaging modalities could lead to more pragmatic implementation.
- Novel molecular imaging modalities have the potential to improve diagnostics and provide new insights into disease pathogenesis.
- Substantially increased and sustained support for basic and translational research is needed to develop and translate novel imaging tools for childhood tuberculosis.

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the sensitivity, specificity, and predictive values of chest radiography for diagnosing tuberculosis. HIV co-infection can confound radiological diagnosis because of the occurrence of other co-infections or HIV-associated diseases, such as lymphocytic interstitial pneumonitis or neoplasia.^{10,11} Therefore, the US National Institutes of Health convened a workshop at the Union World Conference on Lung Health (October, 2018, The Hague, Netherlands) to identify knowledge gaps in imaging approaches and to develop a roadmap for research for childhood tuberculosis.

Currently available imaging tools

Chest radiography is an important tool in the diagnosis of intrathoracic tuberculosis in children,¹² and traditional imaging methods identify surrogates for tuberculosis disease to distinguish it from other pathologies. For example, chest radiography can detect abnormalities compatible with pulmonary, pleural, pericardial, and lymph node disease, which can all be caused by tuberculosis. On the frontal view, chest radiographs can show large lymphadenopathy of the hilar and paratracheal regions and accuracy of diagnoses can be further improved by obtaining an additional view of the lateral chest to visualise subcarinal lymphadenopathy.^{13,14} With the introduction of digital systems, the cost of radiography has decreased substantially and it has become a more feasible option in some resource-limited settings.¹³

However, chest radiography is limited by its two-dimensional representations of three-dimensional anatomy,

resulting in superimposition of structures and difficulties in interpretation.¹⁵ For example, hilar and mediastinal lymphadenopathy is the most frequent—and often the only—manifestation of intrathoracic tuberculosis in children,¹³ yet there is a high level of inter-reader and intra-reader variability for detecting lymphadenopathy on chest radiographs.¹⁶ Studies have also shown that children without detectable abnormalities on chest radiography can have hilar and mediastinal lymphadenopathy on CT scans.^{17,18} Conversely, in some cases, no lymphadenopathy can be found on CT in children with radiographic findings suggestive of lymphadenopathy.¹⁹ It is noteworthy that such lymphadenopathies have been detected on CT scans in children who have been diagnosed with latent tuberculosis infection and then been cured with a preventive treatment regimen for this disease.^{17,20} Considering the continuum of tuberculosis exposure, infection, and disease, whether mildly enlarged hilar and mediastinal lymph nodes that are not supported by clinical or radiological findings represent infection versus active tuberculosis disease is not known.²¹ The imaging characteristics of lymph nodes that are suggestive of active tuberculosis disease and would consequently benefit from a curative treatment regimen (ie, with three or four drugs) have also not been well defined.

The quality of chest radiographs is also variable, with one study finding that only 60% of chest radiographs were of moderate or good quality, despite them being done in a tertiary care university hospital.²² Technical factors also affect the quality of chest radiographs in children—eg,

	Year first commercially available	Performance	Reader variability	Relative cost	Relative radiation exposure	Suitability for use in children	Notes
Conventional imaging							
Radiography	1920s	Low sensitivity and specificity	High	Low	Minimal	High	Could benefit from digital computer-assisted tools
Ultrasonography	1956	Could have increased accuracy for detecting lymphadenopathy	High	Low	None	High	..
Cross-sectional imaging							
CT	1971	High-quality three-dimensional information, high sensitivity and specificity to visualise pathological changes	Low	Moderate	Child-friendly protocols with low radiation exposures available in many settings	Can be performed rapidly (in seconds) within a single breath-hold or with free breathing in young children	Could benefit from digital computer-assisted tools
MRI	1977	Has advanced imaging capabilities beyond anatomical imaging	Low	High	None	Moderate—might need sedation in young children, although short sequence lung MRI is also available	May require special protocols for lung imaging due to air–water interface
Molecular imaging							
SPECT	1999	Functional imaging capable of elucidating lesion pathophysiology	Moderate	Moderate	Moderate	Moderate	..
PET-CT and PET-MRI	2000	Higher sensitivity and spatial resolution than SPECT	Low	High	Moderate	Moderate—rapid imaging feasible	..

SPECT and PET are nuclear medicine tomographic imaging techniques. SPECT uses a gamma camera. SPECT scanners and SPECT compounds are generally cheaper and more widely available than for PET. However, PET is generally more sensitive than SPECT. SPECT=single-photon emission computed tomography.

Table 1: Comparison of currently available tools for tuberculosis imaging in children

young children cannot hold their breath and it is difficult to immobilise them safely, leading to rotation and motion artefacts. Finally, even paediatric radiologists show poor specificity in diagnosing features attributable to tuberculosis,²³ especially in children living with HIV¹⁰ who can have multiple co-infections and pathologies.²⁴ Numerous studies have therefore reported that chest radiography for tuberculosis has poor specificity (<50%) in children.^{10,22,25–27} The available data on the use of computer-aided detection of tuberculosis in children using digital chest radiography, which might be especially challenging in children because of the limitations we have outlined, are not robust enough. However, telereading and deep learning algorithms could automate diagnostic processes, bringing consistency to the detection of pathological features that are suggestive of tuberculosis^{28,29} and provide high-throughput techniques that would be especially useful for screening approaches.³⁰

In addition to radiography, there are several other imaging techniques that have been commercially available for over 20 years (table 1), yet there are relatively few studies that have systematically evaluated their performance (sensitivity, specificity, and predictive value) in the detection of abnormalities indicative of tuberculosis in young children. A brief summary about how available imaging modalities can be used is shown in figure 1. Cross-sectional imaging, such as CT and MRI, generates holistic, three-dimensional, and spatial information to visualise multiple coexisting lesions, thereby enhancing sensitivity and providing non-invasive longitudinal monitoring for the individual.

CT is superior to chest radiography for detecting lymphadenopathy, but might require the administration of intravenous contrast for optimal visualisation, which shows enhancement of lymph nodes in a high proportion of patients with tuberculosis.³¹ It can sometimes be difficult to distinguish hilar and mediastinal lymphadenopathy from normal thymus on CT scan; however, this is also a challenge with interpreting chest radiographs.²⁷ CT also provides better visualisation of airway compression, pneumonia (including expansile pneumonia characterised by increased volume of the involved lobe or segment), lymph node necrosis, and lung necrosis than radiography.^{31–33} Necrosis is often present in childhood tuberculosis and is a well known pathological feature of the disease,³⁴ and therefore detection of necrotic lesions on CT (or MRI) scans is highly suggestive of tuberculosis. A retrospective study showed that CT combined with computer algorithms that detect quantitative image features was helpful in differentiating pulmonary tuberculosis from community-acquired pneumonia in young children (<5 years).³⁵ Serial CT scanning is a good marker of response to tuberculosis treatments in adults.^{36,37} Another study reported that quantitative changes in CT lesion volumes during treatment in adults with multidrug-resistant tuberculosis were predictive of long-term treatment outcomes.³⁸

MRI is an excellent method to detect lymphadenopathy because of its high-spatial resolution and tissue contrast.

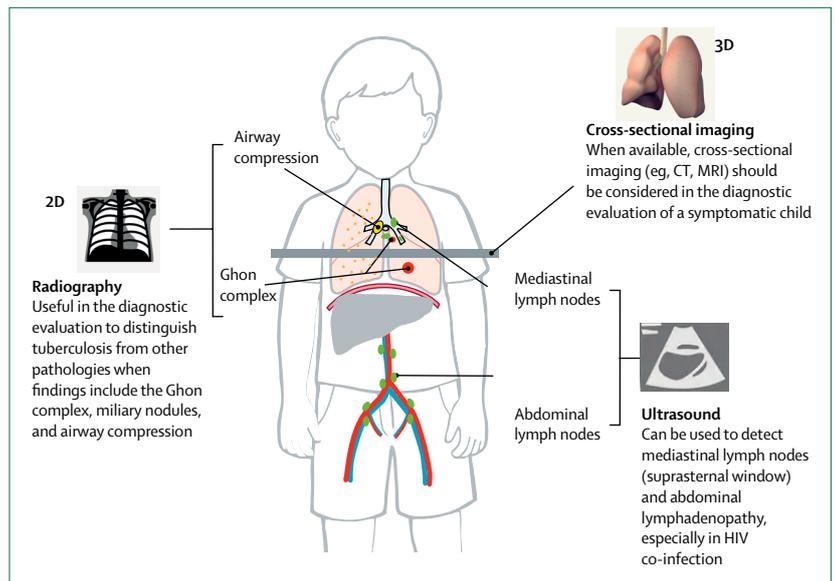


Figure 1: Optimising the use of currently available imaging techniques

Chest radiography interpretation should be limited to findings such as the detection of the Ghon complex, miliary nodules, and airway compression to distinguish tuberculosis from other pathologies. However, because of the low accuracy of chest radiography for detecting pathologies suggestive of tuberculosis, when available, cross-sectional imaging should be considered in the diagnostic evaluation for tuberculosis in a symptomatic child. Additionally, mediastinal and abdominal ultrasound can be used to improve diagnostic accuracy. 2D=two-dimensional. 3D=three-dimensional.

MRI can also detect tissue necrosis well and, as shown in a small study of children, all necrotic tuberculosis lesions showed low T2 signal on MRI.³⁹ Beyond high-spatial resolution and contrast anatomical imaging, MRI also has advanced capabilities such as dynamic contrast-enhanced imaging, magnetic resonance spectroscopy, and chemical exchange saturation transfer contrast. Some of these techniques might not be as rapid as conventional anatomical MRI sequences, and thus require sedation in young children; however, all these techniques could support complementary approaches for molecular imaging of infectious diseases.⁴⁰ Novel MRI techniques have also been shown to differentiate sterile inflammation or oncological processes from bacterial infections in animal models.^{41,42}

Ultrasound has been used to show tuberculosis lymphadenopathy,^{43,44} and protocols using the suprasternal window have detected abnormalities more frequently than radiography.^{45,46} Although ultrasound is radiation-free and a relatively inexpensive technology, it is operator-dependent and thus has variable accuracy. Given that air blocks the transmission of ultrasound waves, visualisation of the hila is not possible through aerated lungs and air-dense regions could also lead to artefacts.^{47,48} Therefore, the suprasternal approach for identifying mediastinal lymphadenopathy might be superior. Importantly, children living with HIV who develop pulmonary tuberculosis are more likely to have abdominal lymphadenopathy, and ultrasound can detect these extrathoracic foci and improve diagnostic accuracy.⁴⁹

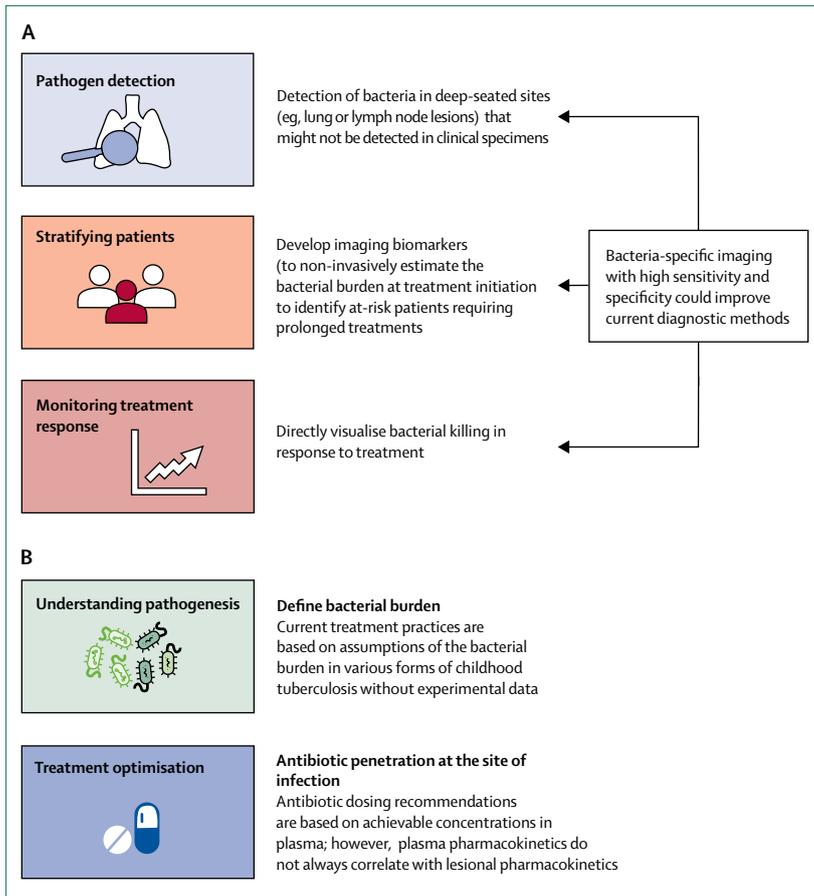


Figure 2: Potential applications of advanced imaging tools

(A) The poor sensitivity of current pathogen detection systems, especially for deep-seated infections (not represented by clinical samples such as blood), could be improved by the development and validation of sensitive pathogen-specific imaging technologies. This approach could also allow patient stratification for rigorous evaluation of new diagnostic tools for childhood tuberculosis and to identify patients requiring longer treatments. Repeated imaging could also help to monitor response to treatments. (B) Much of the understanding of infections stems from clinical samples that might not accurately represent the local biology at infection sites. New platforms for basic research incorporating advanced imaging tools could enable the use of an iterative, bidirectional process to integrate findings from animal models and human studies, as well as to validate and refine animal models so that they can address the relevant human pathobiology. Specific molecular imaging approaches that measure the local biology (bacteria, antibiotic concentrations, and microenvironment) could improve understanding of pathogenesis, mechanisms of novel therapeutics, antibiotic treatments, and serve as biomarkers to measure efficacy and treatment responses.

Ultrasound can also be used to monitor tuberculosis treatment, although it might be difficult to monitor airway disease accurately.⁵⁰

Advanced imaging tools

Much of the understanding of infections stems from clinical samples (blood, urine, stool, or cerebrospinal fluid) that might not accurately represent the local biology at infection sites (figure 2).^{15,51} Imaging technologies, such as PET or single-photon emission computed tomography, can rapidly visualise molecular events deep within the body and have powerfully augmented clinical medicine. Because these technologies are clinically translatable, they allow comprehensive cross-species animal and

human studies to visualise molecular events at a lesional level,^{15,40} which is not feasible with current methods.

Pathogen-specific diagnosis

Traditional imaging tools are based on non-specific changes in anatomy or activity, reflecting a combination of the infection and the host-inflammatory response.¹⁵ Given that the host-response to a pathogen can be highly variable, traditional imaging tools often do not provide an accurate diagnosis.²¹ Several studies suggest that ¹⁸F-fluorodeoxyglucose PET can be highly sensitive for detecting tuberculosis lesions.^{38,52} However, as an analogue of glucose, ¹⁸F-fluorodeoxyglucose is unable to differentiate among oncological, inflammatory, or infectious processes. Furthermore, the goal is to identify the organism and not just detect abnormalities. Therefore, bacteria-specific imaging compounds, such as radioanalogues of para-aminobenzoic acid⁵³ and trehalose,⁵⁴ which target fundamental biochemical differences between bacteria and mammalian cells, have been developed and provide new opportunities to detect *Mycobacterium tuberculosis*.¹⁵ These technologies could be used to address some fundamental questions related to the pathogenesis of childhood tuberculosis. For example, even though childhood tuberculosis is predominantly paucibacillary, children with tuberculosis are treated with a 6-month multidrug treatment regimen designed mainly for adults. Therefore, a pressing research need is to define the total bacterial burden in the spectrum of childhood tuberculosis using pathogen-specific imaging technologies and correlating this burden with clinical presentation and long-term outcomes. Similarly, the poor sensitivities of pathogen-based tests to establish the diagnosis of tuberculosis in children prevent the rigorous evaluation of new diagnostic tools for childhood tuberculosis and the attribution of incorrect clinical and radiological features to the disease. Moreover, most childhood tuberculosis is the result of a primary infection, with higher rates of disseminated, extrapulmonary foci that are more difficult to detect (eg, tuberculous meningitis).²⁷ Pathogen-specific imaging approaches could improve upon the poor sensitivity of current pathogen detection systems and overcome some of these challenges. However, this field is in its early stages and substantial research is needed to validate and apply *M tuberculosis*-specific imaging approaches to childhood tuberculosis.

Antibiotic development

Dosing recommendations for antibiotics continue to be developed on the basis of their achievable concentrations in plasma, although plasma pharmacokinetics do not always correlate with lesional pharmacokinetics at infection sites.⁵⁵ There are major gaps in our understanding of pharmacokinetics for several antibiotics, especially for privileged sites such as the brain and sites with intense tissue necrosis or lymphadenitis. Moreover, drug pharmacokinetics substantially change depending

on the age of the child.⁵⁶ Direct measurement of lesional drug concentrations cannot be achieved in humans except in rare circumstances, and sampling is generally limited to a single accessible lesion. However, imaging with radiolabelled antibiotics can enable non-invasive and simultaneous measurements of drug pharmacokinetics in multiple organ systems and anatomic compartments without biopsy-related artefacts or alterations to tissue physiology. Some of these technologies have already been evaluated in adults with tuberculosis,^{51,55} and similar studies would be feasible in children. PET is available at major referral centres in low-income or middle-income countries,¹⁵ enabling small (ten to 20 participants) studies⁵⁷ to provide detailed and unbiased drug pharmacokinetic data in the populations of interest with disease, without the need for invasive procedures.

Understanding lesional biology

M tuberculosis is known to adapt to its local microenvironment (such as hypoxia or nutrient starvation) and develop a quiescent (so-called dormant) state, which allows the pathogen to evade antibiotics and host-immune responses. Extended antibiotic courses are required to kill this subpopulation of dormant bacteria, although treatments could also be improved by host-directed therapy (HDT) that would alter the local microenvironment to prevent this bacterial adaptation.⁵⁸ Specific molecular imaging approaches that measure the local biology could therefore provide insights into the pathogenesis of *M tuberculosis*, show mechanisms of novel HDTs, and serve as biomarkers to measure efficacy and monitor treatment responses. For example, *M tuberculosis* prevents apoptosis—a host-protective mechanism—leading to necrosis of the infected host-cells.⁵⁹ Necrosis causes tissue destruction, reduces antibiotic penetration, and limits immune cell access to the infected sites. Therefore, pro-apoptotic drugs could be used as an HDT, and non-invasive clinically translatable imaging^{60,61} could be used to monitor lesional apoptotic changes in response to HDTs to support the development of novel treatments.

Precision medicine

Several tuberculosis trials have suggested that 80–85% of adults with drug-susceptible pulmonary tuberculosis are cured with 4 months of standard treatment, but 15–20% will relapse if not treated for at least 6 months.⁶² However, accurate tools to identify patients requiring longer treatments do not exist. By providing information on the total bacterial burden, the location and extent of disease, and the response to treatment, advanced imaging tools using bacteria-specific imaging compounds could identify patients requiring prolonged treatments.⁵ Many cases of multidrug-resistant tuberculosis are not being detected in children because of practical difficulties in isolating the bacteria.⁶³ In the future, developing imaging approaches to detect mutations conferring drug resistance (eg, catalase peroxidase or KatG mutation that

Panel: Knowledge gaps and areas for research in childhood tuberculosis

Optimising clinical care

When to use a given imaging technique?

- Systematic studies comparing chest radiography, ultrasound, and cross-sectional imaging with clinical outcomes
- Development of clinical practice guidelines on when imaging techniques other than chest radiography should be considered

Variability in interpretation of chest radiography

- Development and optimisation of automated, digital (computer-assisted) tools and telereading to streamline interpretation of imaging findings

Poor sensitivity of current pathogen detection systems

- Development and validation of pathogen-specific imaging technologies based on PET, SPECT, and MRI or MRS
- These technologies need to be comprehensively evaluated in animal and human studies to develop robust tools, with strong biological basis

What imaging characteristics are suggestive of active tuberculosis disease and would benefit from a curative treatment regimen?

- Evaluation of traditional and pathogen-specific imaging technologies to phenotype disease and correlation with clinical presentation (in the clinical continuum of exposure–infection–disease) as well as long-term outcomes

Biomarkers to stratify patients needing shorter or longer treatment durations

- Evaluation of advanced imaging techniques to identify patients requiring shorter or longer treatment durations—eg, since bacterial burden at treatment initiation could be a major driver of treatment duration, imaging biomarkers that provide accurate information on the total bacterial burden could be predictive of treatment duration needed to achieve cure
- Cross-species animal and human studies to visualise disease at a lesion level (which are not feasible with current techniques) as a discovery approach for development of novel biomarkers

Advancing basic science

Define the bacterial burden in the clinical spectrum of childhood tuberculosis

- Pathogen-specific imaging technologies to quantify bacterial burden in various forms of childhood tuberculosis

Understanding antibiotic biodistribution at infection sites

- Imaging studies to assess antimicrobial (radiolabelled antibiotics) distribution of new and important existing antibiotics

Validating animal models with human disease

- Imaging studies to integrate data from animals to humans.
- An iterative, bidirectional process to integrate findings from animal models and human studies could allow model refinements, validate animal models, and address the relevant human pathobiology

Increasing implementation

Bias regarding the perceived risk and benefits of advanced imaging

- Educating the public and clinicians about the risks and benefits of using available imaging techniques could lead to more pragmatic implementation.
- Developing a curriculum on advanced tuberculosis imaging

Cost and lack of facilities with advanced imaging techniques

- Impact studies and cost-benefit modelling to determine where advanced imaging will be cost-effective

SPECT=single-photon emission computed tomography. MRS=magnetic resonance spectroscopy.

confers resistance to isoniazid)⁶⁴ and rapidly detect drug-resistant infections in situ could be feasible.

Knowledge gaps and research needs

The key knowledge gaps regarding the use of imaging tools for childhood tuberculosis are outlined in conjunction with a proposed roadmap for future research (panel).

When to use a given imaging modality

Chest radiography is widely used in diagnostic evaluations for tuberculosis in young children; however, published guidelines do not offer clear guidance on when to use other imaging methods.^{12,65,66} Chest radiography interpretation should be limited to specific findings, such as the detection of the Ghon complex, miliary nodules, and airway compression to distinguish tuberculosis from other pathologies.^{10,13,67} However, because chest radiography has low accuracy for detecting pathologies suggestive of tuberculosis, cross-sectional imaging (eg, CT or MRI) should be considered (if available) in the diagnostic evaluation for tuberculosis in a symptomatic child. Additionally, mediastinal and abdominal ultrasound can be used to improve diagnostic accuracy. Automated, computer-assisted tools and telereading could streamline interpretation and perhaps improve accuracy of imaging findings, especially in resource-limited settings with high tuberculosis burden. Systematic studies to assess the added value of these available imaging methods in children with tuberculosis are needed.

How to advance basic science of tuberculosis using imaging modalities?

The poor sensitivity of current pathogen detection systems, especially for deep-seated infections (not represented by clinical samples), could be improved by the development and validation of sensitive pathogen-specific imaging technologies. This approach could also allow patient stratification for rigorous evaluation of new diagnostic tools for childhood tuberculosis and identify patients who require longer treatments. Much of the understanding of infections stems from clinical samples that might not accurately represent the local biology at infection sites.⁵¹ Clinical management is therefore often based on incorrect assumptions using surrogates of tuberculosis disease that do not represent the true underlying biology. For example, rapid bacterial killing and sterilisation are currently considered as the key endpoints for tuberculosis treatments in animal models and clinical trials. However, treatment outcomes in some forms of tuberculosis, such as tuberculous meningitis, could be closely associated with intracerebral host-inflammatory responses, and thus benefit from adjunctive anti-inflammatory treatments.⁶⁸ Imaging biomarkers of inflammation⁶⁹ could be used to monitor lesional inflammatory responses in the same patients before and

during adjunctive anti-inflammatory treatments and support the development of novel treatments. Since genetic factors predict host-inflammatory responses in tuberculous meningitis,^{70,71} imaging biomarkers could also be used to identify patients who would most benefit from adjunctive anti-inflammatory treatments. Similarly, data from adults with tuberculosis suggest that curative treatments might not need to eradicate all *M tuberculosis* bacteria in some patients;⁵⁵ therefore, it would be important to understand the goals of curative antibiotic treatments—eg, sterilisation of lesions or substantial reduction in the bacterial burden. New platforms for basic research incorporating advanced imaging tools could address some of these key knowledge gaps and allow integration of cross-species data from animals to humans that is not feasible with current methods.

Obstacles to the implementation of advanced imaging modalities

Chest CT scans can be done rapidly (ie, in seconds) within a single breath-hold or with free breathing in young children and without the need for sedation or anaesthesia. Child-friendly CT scans can deliver a radiation dose equivalent to only three chest radiograph sets (frontal and lateral combinations).^{5,72} Similarly, MRI is radiation free but generally requires anaesthesia or sedation in young children because of the longer acquisition times, although short-sequence lung MRI has been done in children with pulmonary infections, including tuberculosis, without the need for sedation.⁷³ The mortality risk for patients with multidrug-resistant tuberculosis is similar or higher than 5-year mortality risks due to common cancers,⁷⁴ yet imaging continues to be used for the management of many cancers (even for children) but is avoided in the management of infectious diseases. Unlike ¹⁸F-fluorodeoxyglucose, which is retained by any tissue with increased glycolysis, many PET compounds for infectious diseases in development are rapidly eliminated from the body, substantially reducing radiation exposure and making them safer for children. Focused PET scans can be done in 3–5 min, obviating the need for anaesthesia or sedation. Therefore, a pragmatic approach is needed to surpass the biases regarding the use of imaging technologies for infectious diseases.

Despite advanced imaging tools being relatively expensive and not widely available for low-income and middle-income settings, these countries have witnessed considerable growth in the installation and use of advanced imaging. Additionally, imaging costs are substantially lower in low-income or middle-income nations compared with those in high-income nations. Although, a cyclotron is needed to produce most PET compounds, many PET compounds can be transported locally usually within a 2–3 h travel radius. PET compounds using ⁶⁸Ga can be produced without the need of a cyclotron and thus could be used in remote areas.⁷⁵ Impact studies and

cost–benefit modelling are needed to determine the settings and scenarios where advanced imaging tools are likely to be cost-effective.

Conclusion

Chest radiography continues to be a useful imaging technique for the initial radiological evaluation of children with suspected intrathoracic tuberculosis, but it is important to recognise its limitations. Imaging methods, such as ultrasound and CT scans, can improve the diagnostic accuracy and should be considered in the examination of a symptomatic child being evaluated for tuberculosis. Educating the public and clinicians about the risks and benefits of using available imaging methods could lead to more pragmatic implementation. Novel molecular imaging techniques have the potential to improve diagnostics and provide novel insights into disease pathogenesis. Finally, substantially increased and sustained support for basic and translational research is needed to develop and translate novel imaging tools for childhood tuberculosis.

Contributors

SKJ and CMP-V contributed equally. SKJ, SAnd, and CMP-V wrote the initial draft. SKJ collated input from all other authors. SKJ, SAnd, PG, and SAnt provided formal content for the workshop. DG-P, CD, and PJ-P were additional panel discussants. AAO reviewed the manuscript and designed the figures. AAO and CMP-V helped in formulating the table and panel. CMP-V, JRS, PJ-P and RSB were part of the conceptualisation team. RSB also helped in organising the panel and post-meeting discussions

Declaration of interests

SKJ reports grants from US National Institutes of Health (NIH) and grants from US Department of Defense's Congressionally Directed Medical Research Programs, during the conduct of the study; SKJ has a pending patent (PCT/US13/059897) on bacteria-specific labelled substrates as imaging biomarkers, filed by Johns Hopkins University. JRS is a member of a Data Safety Monitoring Board for Otsuka Pharmaceuticals for the paediatric pharmacologic studies of delamanid, a new drug used for multidrug-resistant tuberculosis. AAO has a patent pending (PCT/US13/059897) on bacteria-specific labelled substrates as imaging biomarkers, filed by Johns Hopkins University. The views expressed by speakers and panellists at the Department of Health and Human Services (DHHS) sponsored workshops do not necessarily reflect the official policies of the DHHS. SKJ and AAO also receive support from the NIH (Director's Transformative Research Award R01-EB020539, R01-HL131829, R01-EB025985, R01-AI145435-A1, and R21-AI149760), the Department of Defense's Congressionally Directed Medical Research Programs PR-171338P1. SAnt receives support from the Intramural Research Program of the National Library of Medicine, NIH. All other authors declare no competing interests.

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