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TUBERKULOSE BEI KINDERN UND JUGENDLICHEN

IN LÄNDERN MIT NIEDRIGER TUBERKULOSEINZIDENZ

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Abkürzungsverzeichnis

AUC	Area under the curve
BCG	Bacille Calmette Guérin
C_{max}	Maximale Serumkonzentration
CT	Computertomographie
ECDC	European Centre for Disease Prevention and Control
ELISPOT®	enzyme-linked immuno spot assay
EMB	Ethambutol
ESPID	European Society for Paediatric Infectious Diseases
FDA	US Food and Drug Association
GCS	Glasgow Coma Scale
IGRA	Interferon-gamma release assay
INF-γ	Interferon-gamma
INH	Isoniazid
KG	Körpergewicht
LTBI	Latente tuberkulöse Infektion
M. tuberculosis	*Mycobacterium tuberculosis*
MRT	Magnetresonanztomographie
NTM	Nicht-tuberkulösen Mykobakterien
PentID	Paediatric infectious diseases network
ptbnet	Paediatic tuberculosis network european trialsgroup
PZA	Pyrazinamid
RKI	Robert Koch Institut
RMP	Rifampicin
TB	Tuberkulose
TBM	Tuberkulöse Meningitis
THT	Tuberkulin-Haut-Test
T_{max}	Zeit bis zur maximalen Serumkonzentration
TNF-α	Tumornekrosefaktor-alpha
UTRCD	Uniform TBM Research Case Definition
WHO	World Health Organization

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1 Einleitung

1.1 Epidemiologie der Tuberkulose bei Kindern und Jugendlichen

Nach Schätzungen der Weltgesundheitsbehörde (World Health Organization, WHO) ist ein Viertel der Weltbevölkerung mit Tuberkulose (TB) infiziert, wovon im Jahr 2020 weltweit etwa 10 Millionen Menschen an TB erkrankten, davon 1,1 Millionen Kinder (1). Aufgrund von Herausforderungen in der Diagnosestellung bei Kindern und einer häufig nur unzureichenden Registrierung pädiatrischer Tuberkulosefällen ist davon auszugehen, dass diese Zahl weit unter der tatsächlichen Erkrankungshäufigkeit liegt. Kinder machen 15-20% der TB-Fälle in Hochrisiko-Ländern aus, ein Anteil, der in manchen Regionen auf bis zu 40% steigen kann (2). Die niedrige Bakterienlast bei Kindern mit TB (Pauzibazillarität) mit dem damit einhergehenden verminderten Ansteckungsrisiko hat unter anderem dazu geführt, dass Kinder im Kampf gegen TB weniger priorisiert wurden (3, 4). Erst seit dem Jahr 2012 wurden pädiatrische TB-Fälle und an TB verstorbene Kinder in den TB-Jahresbericht der WHO mit aufgenommen. Im Jahr 2020 betonte die WHO die Notwendigkeit, die Informationsqualität zu TB bei Kindern zu erhöhen und damit die Falldefinition und die Abbildung der tatsächlichen Fallzahlen zu verbessern. Die Tuberkuloseinzidenz in Deutschland im Jahr 2020 betrug 5,0 Neuerkrankungen pro 100.000 Einwohner, wobei die Zahlen 2015 im Rahmen der Flüchtlingskrise deutlich zugenommen hatten (7,3/100.000, ein Plus von 29% zum Vorjahr) und dann langsam rückläufig waren (5). Bei ausländischen Staatsangehörigen war die Inzidenz mit 24,6 pro 100.000 Einwohner (ähnlich in den Vorjahren) etwa 14 Mal so hoch wie in der deutschen Bevölkerung (Inzidenz 1,8) (5). 2020 erkrankten 163 Kinder und Jugendliche unter 15 Jahren an einer TB (1,4 pro 100.000 Kinder). Das Erkrankungsrisiko zeigte eine Altersabhängigkeit, wobei die höchste Inzidenz bei Kleinkindern verzeichnet wurde (Inzidenz 2,1/100.000 Kinder bei Kindern < 5 Jahren, 0,8/100.000 bei Kindern 5-9 Jahre und 1,3/100.000 bei den 10-14-Jährigen). Die Inzidenz bei Kindern mit ausländischer Staatsangehörigkeit war im Vergleich zu deutschen Kindern etwa 12-mal so hoch (Inzidenz 6,6 versus 0,5/100.000 Kinder) (5). Das am häufigsten betroffene Organ war auch im Kindesalter die Lunge (124/163 Fällen). Die häufigste extrapulmonale TB-Form war die Lymphknoten-TB. Bei zwei Kindern wurde 2020 eine tuberkulöse Meningitis (TBM) diagnostiziert. Ein Säugling verstarb in Folge einer Lungen-TB (5).

1.2 „End TB Strategy“ der Weltgesundheitsbehörde (WHO)

Im Rahmen der immensen globalen Herausforderung hat die WHO im Jahre 2014 ein ambitioniertes Programm zur Elimination der TB vorgestellt: die „End TB strategy“ (6). Ziel dieser Strategie ist es, zum Jahre 2035 weltweit die Zahl der TB-Toten um 95% und die TB-Inzidenz um 90% zu senken. Um diese Ziele zu erreichen, müsste sich die Abnahme der globalen TB- Inzidenz von jährlich 2% in 2015 auf 10% in 2025 steigern und die Zahl des Anteils der Erkrankten, die versterben, von 15% in 2015 auf 5% in 2025 senken. Dafür bedarf es besserer diagnostischer Tests, insbesondere neuer „point-of-care-tests“, sicherer, einfacherer und kürzerer Therapieregime sowohl für die Erkrankung als auch die latente tuberkulöse Infektion (LTBI) und effektive Impfungen prä- und post-Exposition (6). Da sich die Herausforderungen und Ziele bei der Bekämpfung der TB zwischen Ländern mit hoher TB-Inzidenz und meist niedrigem Einkommen und Ländern mit niedriger Inzidenz und meist höherem Einkommen unterscheiden, hat die WHO einen Aktionsrahmen für Niedriginzidenzländer publiziert (7). Niedriginzidenzländer sind dabei als Länder definiert, bei denen die TB-Inzidenz <10 TB Fälle pro 100.000 Einwohner liegt. Ziel ist es, zunächst bis 2035 eine „Prä-Elimination“ mit weniger als 1 TB-Fall pro 100.000 Einwohner und 2050 eine Elimination der TB als Gesundheitsproblem (<1 TB-Fall pro 1 Mio. Einwohner) zu erreichen (7). In Deutschland ist dafür ist eine jährliche Abnahme der Inzidenz von 10% notwendig. Besonderes Augenmerk wird dabei neben der optimierten Therapie der TB auf den präventiven Bereich gerichtet. Dabei wird das gezielte Screening von Risikogruppen, insbesondere Asylsuchenden wie auch das Management der LTBI als wichtiger Bestandteil einer erfolgreichen TB-Kontrolle anerkannt. Die LTBI stellt ein anhaltendes Erregerreservoir dar und deren Bekämpfung ist entscheidend für das Ziel einer TB-Elimination. Allein die hohe Zahl von TB-infizierten Individuen (1,7 Milliarden) weltweit wird das Erreichen der globalen Ziele zur Eliminierung der TB verhindern, wenn keine Maßnahmen ergriffen werden (8).

1.3 Klinisches Bild der Tuberkulose bei Kindern und Jugendlichen

1.3.1 Pathogenese

Die häufigste Erkrankungsform ist die pulmonale TB. Die pulmonale Infektion mit *Mycobacterium tuberculosis (M. tuberculosis)* erfolgt, wenn 1-5µm große Aerosolpartikel, die sogenannten „droplet nuclei“, die nur wenige Erreger enthalten, eingeatmet werden und sich

in den terminalen Atemwegen ablagern. Durch Aktivierung von Alveolarmakrophagen, Neutrophilen und dendritischen Zellen kommt es zur Freisetzung verschiedener Zytokine, Chemokine und antimikrobieller Peptide. Die aktivierten dendritischen Zellen migrieren zu den lokalen Lymphknoten und Stimulieren die Differenzierung von Typ1-T-Helferzellen, welche die Zytokine Interferon-gamma (INF-γ) und Tumornekrosefaktor-alpha (TNF-α) freisetzen. Diese tragen zur weiteren Aktivierung von Makrophagen und dendritischen Zellen bei und führen zur Begrenzung der Infektion und schließlich zur Granulombildung (9). Im Rahmen dieser lokalen Abwehr entsteht der sogenannte meist pleuraständige Primärfokus oder „Ghon Fokus“ und nach Ausbreitung in Lymphknoten der sogenannte Primärkomplex. Der Primärfokus heilt häufig unter Kalzifizierung komplett aus und ist radiologisch meist nur 4-8 Wochen nach Infektion nachweisbar. Bereits sehr frühe Studien konnten jedoch zeigen, dass es zu einer Erregerpersistenz in den Lymphknoten, v.a. denen des Angulus venosus kommt (10). Nach dieser ersten Phase nach Infektion, in der auch die immunologischen Tests zur TB-Diagnostik positiv werden, folgt nach 1-3 Monaten die nächste Phase, in der eine hämatogene Ausbreitung stattfinden kann. Dies ist die Phase mit dem höchsten Risiko für schwere Manifestationen wie der TBM und der Miliar-TB. Typische Krankheitsbilder der sich anschließenden Phase nach 3-9 Monaten ist der tuberkulöse Pleuraerguss bei älteren Kindern und parenchymatösen oder Lymphknotenmanifestationen bei Kindern unter 5 Jahren. Spätere Manifestationen der TB 1-3 Jahre nach Infektion sind die osteo-artikuläre TB bei Kindern <5 Jahren und die postprimäre pulmonale TB (meist Kinder >10 Jahre), die dem Bild der Erwachsenen-TB mit typischer Beteiligung der apikalen Segmente der Lungenoberlappen („Simon’schen Spitzenherden“) entspricht (11). Der Verlauf der Erkrankung wird dabei durch das Gleichgewicht zwischen der Immunität des Wirtes und der Pathogenität des Erregers bestimmt. Dieses Gleichgewicht zeigt eine starke Altersabhängigkeit. Während es bei Kindern <1 Jahr ohne Therapie in 50% der Fälle zu einer Erkrankung nach Infektion kommt und bei 10-20% zu einer schweren, disseminierten Form (TBM, Miliar-TB), sinkt das Erkrankungsrisiko im weiteren Kindesalter deutlich und beträgt bei den 5-10-Jährigen nur etwa 2%. Im Jugendalter (>10 Jahre) kommt es zu einer erneuten Zunahme des Erkrankungsrisikos auf 10-20%. Die Lungen-TB stellt in allen Altersklassen die häufigste Manifestation dar (11). Entsprechend ist die Mortalitätsrate im jungen Kindesalter am höchsten. Diese betrug in der Ära vor Chemotherapie insgesamt 21,9% mit einer signifikant erhöhten Mortalitätsrate bei den 0-4-Jährigen (43,6%) im Vergleich zu den 5-14-jährigen (14,9%) (12). Nach Zugang zu einer

Chemotherapie konnte die Mortalitätsrate deutlich gesenkt werden und lag insgesamt bei 0,9% (2,0% bei den 0-4-Jährigen) (12).

1.3.2 Klinische Manifestationsformen

Hierbei werden nur die für diese Schrift relevanten Manifestation dargestellt.

1.3.2.1 Latente tuberkulöse Infektion

Unter einer LTBI versteht man den immunologischen Nachweis einer TB-Infektion ohne radiologische oder klinische Symptomatik. Eine LTBI ist dabei als ein Kontinuum zwischen Erregerelimination und asymptomatischer, nichtsdestotrotz aktiver Tuberkulose zu verstehen (13). Nach Infektion besteht bei Erwachsenen ein lebenslanges Risiko von 5-10% für einen Progress zu einer Erkrankung, wobei das Risiko generell in den ersten 2 Jahren nach Infektion am höchsten ist (14, 15). Für Kinder wurde eine deutlich höhere kumulative 5-Jahres-Progressionsrate nach TB-Exposition beschrieben: 33,3% bei Kindern <5 Jahren und 19,1% bei Kindern im Alter von 5-14 Jahren (16). Weltweit ist ca. ein Viertel der Bevölkerung latent infiziert (8).

1.3.2.2 Pulmonale Tuberkulose

Das klinische Bild einer pulmonalen TB ist initial häufig unspezifisch. Etwa die Hälfte der Kinder, bei denen im Rahmen einer Umgebungsuntersuchung radiologisch eine pulmonale TB diagnostiziert wird, haben im Frühstadium keine oder nur wenige Symptome. Hinweisend auf eine pulmonale TB können persistierender Husten, Gewichtsverlust, Fieber und Fatigue sein (17). Kommt es zu Komplikationen wie Bronchuskompression mit Dys- oder Atelektasenbildung, Lymphknoteneinbrüchen oder Kavernenbildung („komplizierte pulmonale TB“) können entsprechend weitere Symptome auftreten.

1.3.2.3 Tuberkulöse Meningitis

Die TBM macht nur 1% aller TB-Formen aus, hat aber eine höhere Mortalitäts- und Morbiditätsrate als jede andere TB-Erkrankung. Ein Auftreten ist in jedem Lebensalter möglich, Kinder im Alter von 2-4 Jahren sind aber am häufigsten betroffen (18). In frühen Autopsiestudien zeigte sich bei der Mehrzahl der Kinder kleine Granulome im Hirnparenchym oder den Meningen (sogenannte „Rich-Foci“). Es wurde postuliert, dass eine TBM durch

Ruptur der Granulome und damit Freisetzung der Mykobakterien in den subarachnoidalen Raum entstünde (19). Neuere Studien zeigen, dass die Disseminierung im Rahmen einer Miliar-TB einen wichtigen Anteil an der Pathogenese einer TBM hat (20). Dennoch bleibt die genaue Pathogenese und vor allem die Überwindung der Blut-Hirn-Schranke durch Mykobakterien noch unklar. Es kommt nach Übertritt der Blut-Hirn-Schranke zu einer TH1-vermittelten Immunreaktion, die sowohl zu einem direkten Parenchymschaden als auch zu einer obliterierenden Endarteriitis führen kann (5). Betroffen sind vor allem die basalen Leptomeningen.

Die initialen Symptome der TBM sind häufig sehr unspezifisch und eine frühzeitige Diagnosestellung damit erschwert. Insbesondere jüngere Kinder aus Niedriginzidenzländern haben ein erhöhtes Risiko für eine verspätet gestellte Diagnose mit desaströsen Folgen (21). TBM manifestiert sich meist als eine subakute Meningitis mit frühen Symptomen wie Husten, leichtes Fieber, Erbrechen, Gewichtsverlust, Spielunlust und Abgeschlagenheit, die jedoch typischerweise persistieren. Meningitiszeichen fehlen initial häufig. Ein plötzlicher, akuter Krankheitsbeginn mit neurologischen Auffälligkeiten wie Krampfanfällen oder Paresen ist selten. Ohne Therapie kommt es im Verlauf zum Vollbild einer schweren Meningitis.

Die Schwere der TBM wird klinisch anhand der modifizierten British Medical Research Council-Kriterien klassifiziert, wobei spätere Stadien mit einem schlechteren Outcome assoziiert sind (18, 22-24):

- Stadium I: Glasgow Coma Scale (GCS) 15 Punkte, kein neurologisches Defizit
- Stadium II: GCS 11-14 Punkte oder GCS 15 Punkte mit fokalen neurologischen Defiziten
- Stadium III: GCS <11 Punkte, ausgeprägte neurologische Defizite (25).

Das Ausmaß des ischämischen Parenchymschadens und das daraus resultierende schlechte Outcome bei Kindern mit TBM wird neben den Liquorzirkulationsstörungen mit Ausbildung eines Hydrocephalus vor allem durch die ausgeprägte Vaskulitis bedingt (25). Bei etwa 1/3 der Kinder mit schwerer Meningitis kommt es zu Hirninfarkten, bilaterale symmetrische Infarkte der Basalganglien sind besonders charakteristisch (26). Das Ausmaß der Vaskulitis wird auch durch eine adäquate antituberkulöse Therapie nicht beeinflusst, so dass von einem immunologischen Phänomen auszugehen ist (27). Weitere Komplikationen sind intracerebrale Tuberkulome oder selten tuberkulöse Pseudo-Abszesse. Sehr häufig (85% d. F.) kommt es zu einer Hyponatriämie entweder als Folge des Syndroms der inadäquaten Sekretion antidiuretischen Hormons oder durch ein cerebrales Salzverlustsyndrom (28).

1.4 Diagnostik der Tuberkulose bei Kindern und Jugendlichen

1.4.1 Anamnese

In Niedriginzidenzländern gibt die Anamnese einen wichtigen Hinweis für die Einleitung weiterer Diagnostik bezüglich einer TB. Die Möglichkeit eines Kontaktes zu TB-Patient*innen oder Personen mit hohem TB-Risiko sollte gezielt erfragt werden. Die Herkunft des Kindes oder eines Familienmitgliedes aus einem Hochinzidenzland oder ein dortiger Aufenthalt stellt ebenfalls einen Risikofaktor für eine TB dar (25). Bei der Diagnostik sind ein möglicher Immundefekt (angeboren oder erworben), eine Immunsuppression, der BCG-Impfstatus (BCG=Bacille Calmette Guérin) und Faktoren bezüglich des Indexfalles wie Infektiosität oder Resistenzprofil zu beachten (25).

1.4.2 Immunologische Tests

Bei den zur Diagnostik der TB herangezogen immunologischen Tests wird die charakteristische Immunantwort auf Kontakt mit *M. tuberculosis*-Antigenen gemessen. Diese Tests reagieren erst mit einer Latenz von mehreren Wochen, typischerweise ist ein positives Ergebnis nach 4-7 Wochen zu erwarten (29).

Der älteste Test ist der Tuberkulin-Haut-Test, bei dem 0,1 ml Tuberkulin (in Deutschland PPD-RT23 des Statens Serum Instituts Kopenhagen) streng intrakutan (im deutschsprachigen Raum traditionell volar am linken Unterarm) injiziert werden. Bei vorangegangenem Kontakt mit mykobakteriellen Antigenen kommt zu einer Typ IV-Hypersensitivitätsreaktion. Nach 48-72 kann die Induration abgelesen werden. Die Sensitivität hängt von der Größe der Induration ab und liegt zwischen 67-91%. Die Spezifität wird insbesondere durch das Alter, eine frühere BCG-Impfung und eine eventuelle Immundefizienz beeinflusst (30, 31). Eine vorangegangene BCG-Impfung sowie eine Kreuzreaktivität mit nicht-tuberkulösen Mykobakterien (NTM) können zu einem falsch-positiven Ergebnis führen. Eine Übersichtsarbeit, die mehr als 240.000 Kinder einschloss, konnte aber zeigen, dass ≥10 Jahre nach BCG-Impfung -verabreicht innerhalb des ersten Lebensjahres- in nur 1% ein falsch-positives Ergebnis vorlag (32).

Als spezifischere immunologische Tests stehen die Interferon gamma release assays (IGRAs) zur Verfügung, welche nicht kreuzreagierend mit BCG und den meisten NTMs sind. Kommerziell sind aktuell der QuantiFERON-TB Gold®, bzw. der Nachfolgetest QuantiFERON-

TB Gold Plus® sowie der enzyme-linked immuno spot assay (ELISPOT®) verfügbar. Bei diesen Tests wird die resultierende INF-γ-Produktion der Gedächtnis-T-Zellen gemessen und das Ergebnis in IU/ml (QuantiFERON-TB Gold®) oder in der Anzahl der INF-γ-produzierender Spots angegeben (ELISPOT TB®). In Metaanalysen wird die Sensitivität für eine „aktive" TB mit 62-76% für den T-SPOT.TB und 70-83% für den QuantiFERON- TB Gold® angegeben mit einer sehr hohen Spezifität von >90% (33, 34).

Weder der THT noch die IGRAs können zwischen einer Infektion und einer Erkrankung unterscheiden, die Höhe der INF-γ-Produktion ist jedoch mit dem Ausmaß der *M. tuberculosis*-Exposition und einer TB assoziiert (35). Vielversprechende neuere ex-vivo Tests, wie der TB flow assay, verwenden weitere Biomarker, die nach Stimulation mit TB-Antigenen von T-Zellen exprimiert werden. In einer ersten Studie gelang mittels TB flow assay die Diskriminierung einer LTBI von einer „aktiven" Erkrankung bei erwachsenen Patienten (36).

1.4.3 Nachweis von *M. tuberculosis*

Aufgrund der Pauzibazillarität und der häufig fehlenden Sputumexpektoration gelingt der mikrobiologische Nachweis von *M. tuberculosis* bei Kindern deutlich seltener als bei Erwachsenen. Neben spontan expektoriertem Sputum eignen sich auch induziertes Sputum oder Magensaft-Aspirat für die primäre Diagnostik einer pulmonalen TB. Die Untersuchung von Nasopharyngealsekret und Stuhl gewinnt zunehmend an Bedeutung (s.u.). Eine bronchoalveoläre Lavage ist selten und dann nur zusätzlich indiziert. Bei extrapulmonaler TB erfolgt zusätzlich die Untersuchung entsprechender Proben vom Ort der Infektion.

Der mikroskopische Nachweis von *M. tuberculosis* bei Kindern mit pulmonaler TB gelingt sehr selten, der kulturelle oder molekulare Nachweis nur in 20-40% (37). Dennoch sollte der Nachweis immer angestrebt werden. Für den kulturellen Nachweis stehen Flüssig- und Festmedien zur Verfügung. In den letzten Jahren haben molekulare Nachweisverfahren an Bedeutung gewonnen, die neben dem PCR-Nachweis von *M. tuberculosis* auch eine Rifampicin (RMP)-Resistenz innerhalb kürzester Zeit nachweisen können. In den aktuellen WHO-Empfehlungen wird die Anwendung des Xpert® MTB/RIF Ultra sogar als initialer Test für die TB Diagnostik und den Nachweis einer RMP-Resistenz aus Sputum und Magensaft und auch Nasopharyngealsekret oder Stuhl empfohlen (38).

1.4.4 Bildgebung

In der Regel ist eine Röntgenaufnahme in p.a.-Projektion ausreichend. Im Gegensatz zu Erwachsenen mit postprimärer TB finden sich bei Kindern Pathologien häufig im Mittellappen, im anterioren Oberlappensegment und den Unterlappen. Initial ist jedoch meist nur eine hiläre oder paratracheale Lymphadenopathie auffällig. Nach den kürzlich veröffentlichen WHO-Leitlinien wird eine pulmonale „non-severe" TB radiologisch von einer „severe" TB unterschieden. Unter eine „non-severe" TB fallen: periphere Lymphknoten-TB, intrathorakale Lymphknoten-TB ohne Bronchusobstruktion, unkomplizierte TB-Pleuritis und eine nicht-kavernöse Erkrankung, die sich auf einen Lungenlappen beschränkt und kein miliares Bild aufweist (38). Zunehmende Bedeutung in der Diagnostik der pulmonalen TB bei Kindern gewinnt die Sonographie (39, 40). Schnittbildgebende Verfahren wie Computertomographie (CT) oder Magnetresonanztomographie (MRT) der Lunge sind spezifischen Fragestellungen vorbehalten und nicht Teil der Routinediagnostik.

1.4.5 Diagnostik bei tuberkulöser Meningitis

Häufig wird die Diagnose einer tuberkulösen Meningitis verzögert gestellt, da die Klinik initial unspezifisch ist, es sich v.a. in Niedriginzidenzländern um ein seltenes Krankheitsbild handelt und immunologische Tests bei schwerer Erkrankung negativ ausfallen können. Typisch sind in der Liquordiagnostik eine lymphozytäre Pleozytose (<500 Zellen/µl), erniedrigte Liquorglukose (<2,2 mmol/l) und ein erhöhtes Liquorprotein (>0,5-5,0 g/l) (25). Selten kann bei akutem Verlauf eine höhere Zellzahl und ein Überwiegen polymorphkerniger Zellen vorliegen, was die Diagnose weiter erschwert. Die Mykobakterienkultur hat zwar eine Sensitivität von 60-70% bei Erwachsenen, doch dauert das Kulturergebnis zu lange für die akute Diagnosestellung (41). Aufgrund der meist geringen Erregerlast und der verminderten Menge an entnommenem Liquor im Vergleich zu Erwachsenen ist die Sensitivität der Kultur bei Kindern geringer (42). Neue molekulare Verfahren (Xpert® MTB/RIF Ultra) zeigten bei Kindern mit TBM ebenfalls nur eine Sensitivität von 50% während bei Erwachsenen die Sensitivität zwischen 76-92% liegt (43). Der negative prädiktive Wert der molekularen Verfahren ist in allen Altersgruppen zu niedrig, um eine TBM damit ausschließen zu können (44). Ein Standard-MRT inkl. T1-gewichteter Sequenz nach Kontrastmittelgabe ist die Bildgebung der Wahl bei TBM (45, 46). Hiermit können typische Pathologien wie basales

Enhancement als auch Komplikationen wie Infarkte, Hydrocephalus oder Tuberkulome detektiert werden (47, 48).
Die Anwendung immunologischer, kultureller und molekularer Diagnostika wurde in wenigen Studien bei Kindern aus Hochprävalenzländern untersucht, Daten zu Niedriginzidenzländern fehlen bislang (18, 49).

1.5 Therapie der Tuberkulose bei Kindern und Jugendlichen

1.5.1 Chemoprophylaxe

Bei der Chemoprophylaxe handelt es sich um eine medikamentöse Therapie, die bei TB-exponierten Personen angewendet wird, die keinen Hinweis für eine TB-Infektion aufweisen (25). Eine Chemoprophylaxe ist aufgrund des hohen Progressionsrisikos generell bei Kindern <5 Jahren empfohlen und sollte bei älteren Kindern mit erhöhtem Risiko (z.B. Immunsuppression, HIV-Infektion) erwogen werden. Die Chemoprophylaxe erfolgt mit Isoniazid (INH), wenn der Indexfall keine INH-Resistenz aufweist. Eine erneute immunologische Testung erfolgt acht Wochen nach dem letzten Kontakt mit dem Indexfall. Fällt diese weiterhin negativ aus, kann die Chemoprophylaxe beendet werden (25).

1.5.2 Chemoprävention

Besteht eine LTBI, ist bei Kindern und Jugendlichen generell die Gabe einer Chemoprävention empfohlen, um einen Progress zu einer TB zu verhindern. Im deutschsprachigen Raum wird bei einem Indexfall mit sensibler TB entweder eine Therapie mit INH für 6-9 Monate oder eine Kombinationstherapie von INH und RMP über 3 Monate verwendet. Bei INH-Resistenz oder INH-Unverträglichkeit des Indexfalles kann alternativ eine Therapie mit RMP über 4 Monate erfolgen (25). Im Rahmen der „End TB Strategie“ ist die LTBI-Therapie in den Fokus gerückt, über deren Anwendung bei Kindern im deutschsprachigen Raum lagen bislang keine Daten vor.

1.5.3 Chemotherapie

Die antituberkulöse Therapie ist immer eine Kombinationstherapie. Bei unkomplizierter, sensibler TB wird bei Kindern standardmäßig eine Dreifachkombination aus INH, RMP sowie

Pyrazinamid (PZA) verwendet, bei unklarer Resistenzlage oder komplizierter TB eine Vierfachtherapie mit zusätzlich Ethambutol (EMB). Nach einer Initialphase von i.d.R. 2 Monaten erfolgt die Deeskalation auf die Erhaltungstherapie, welche standardmäßig mit INH und RMP fortgeführt wird. Während bislang eine Therapiedauer von 6 Monaten empfohlen wurde, konnte im „SHINE-trial“ gezeigt werden, dass bei „non-severe disease“ (s.o.) eine Therapiedauer von 4 Monaten bei Kindern >3 Monaten und <16 Jahren ausreichend ist und wird entsprechend in den aktuellen WHO-Leitlinien empfohlen (38, 50).

Zur optimalen Therapie der TBM gibt es wenig Evidenz (51). In nationalen und internationalen Empfehlungen werden neben INH, RMP und PZA für die Initialphase EMB, Ethionamid, bzw. Prothionamid, oder ein Aminoglykosid empfohlen (25). Aufgrund der besseren Liquorgängigkeit und der oralen Verfügbarkeit wird in Deutschland anstatt EMB Prothionamid in der Initialphase empfohlen (25). Da RMP nur bei vorhandener meningealer Inflammation liquorgängig ist, wird die Erhaltungstherapie quasi als INH-Monotherapie fortgeführt (51). Dies ist v.a. in Regionen mit hoher INH-Resistenz äußerst problematisch. In der aktualisierten WHO-Empfehlungen wird eine intensivierte, 6-monatige Therapie mit INH, RMP, PZA und ETH als gleichwertig zu der bislang empfohlen Therapie mit INH/RMP/PZA/EMB für 2 Monate gefolgt von INH/RMP für 10 Monate gesehen (38).

Für eine optimale Medikamentendosierung bei Kindern müssen spezifische Veränderungen während des Wachstums bedacht werden, die sowohl die Absorption, Distribution, Metabolisierung und Exkretion von Medikamenten betreffen (52, 53). Da sich die Prinzipien der antituberkulösen Therapie zwischen Kindern und Erwachsenen nicht unterscheiden, sollten bei Kindern dieselben Serumkonzentrationen wie die, die bei Erwachsenen eine gute Effektivität gezeigt haben, angestrebt werden. Eine Dosierung basierend allein auf dem Körpergewicht (mg/kg KG) birgt dabei das Risiko einer Unterdosierung der antituberkulösen Therapie, wie wir es bereits in frühen Pharmakokinetik-Studien für INH und EMB zeigen konnten (54-56).

1.6 Bedeutung von Netzwerken in der Diagnostik und Therapie der Tuberkulose in Niedriginzidenzländern – ptbnet

In Niedriginzidenzländern ist die Inzidenz von TB im Kindesalter zu gering, um monozentrisch Studien mit einer ausreichenden Fallzahl durchzuführen. Um die Diagnostik und Therapie in

diesem Setting weiter erforschen und optimieren zu können, ist eine nationale und internationale Kooperation von entscheidender Bedeutung. Das ptbnet (paediatic tuberculosis network european trialsgroup) ist ein internationales Netzwerk von Kinderärzten, die klinisch orientierte Forschung auf dem Gebiet der TB im Kindesalter durch den Austausch und die Entwicklung von Ideen und Forschungsprotokollen fördern. Ziele sind, das Verständnis der pädiatrischen Aspekte der aktiven und latenten TB zu verbessern, die Zusammenarbeit für wissenschaftliche Studien innerhalb Europas zu vereinfachen, Expertise in Wissenschaft und Lehre zu vermitteln, die medizinische Versorgung innerhalb Europas zu harmonisieren und eine evidenzbasierte Grundlage für die Diagnose und Behandlung der TB im Kindesalter zu generieren (http://www.tb-net.org/index.php/ptbnet). Ptbnet ist der pädiatrische Zweig des TBnet und arbeitet mit diesem sowie der „European Society for Paediatric Infectious Diseases“ (ESPID) und dem europäischen „Paediatric infectious diseases network“ (PentID) eng zusammen.

2 Fragestellungen

1. Wie sind die Durchführbarkeit und Ergebnisse eines Tuberkulosescreenings bei minderjährigen Flüchtlingen im Rahmen der Flüchtlingskrise von 2015 als Beispiel einer vulnerablen Gruppe und der Verlauf bei positivem IGRA-Test?

2. Wie werden in den Niedriginzidenzländern Deutschland, Österreich und der Schweiz Diagnostik, Therapie und Management einer LTBI bei Kindern durchgeführt?

3. Wie sind die Serumspiegel von RMP nach oraler Gabe bei Kindern mit pulmonaler TB in unterschiedlichen Altersgruppen?

4. Wie ist die Sensitivität von immunologischen, mikrobiologischen und molekularen Tests bei Kindern mit TBM im Rahmen der klinischen Routine in Europa und welche klinischen und radiologischen Befunde liegen bei Krankenhausvorstellung vor?

5. Wie erfolgt die Therapie bei Kindern mit TBM im Rahmen der klinischen Routine in Europa und wie ist das Outcome?

3 Eigene Arbeiten

3.1 Screening und Therapie der Tuberkulose in einer Berliner Kohorte unbegleiteter minderjähriger Flüchtlinge

***Stephanie Thee**, Renate Krüger, Horst von Bernuth, Christian Meisel, Uwe Kölsch, Valerie Kirchberger, Cornelia Feiterna-Sperling. Screening and treatment for tuberculosis in a cohort of unaccompanied minor refugees in Berlin, Germany. PLoS ONE 14(5): e0216234. https://doi.org/10.1371/journal.pone.0216234*

Im Rahmen der Flüchtlingskrise 2015 kamen 4062 Kinder und Jugendliche ohne Begleitung einer sorgeberechtigten Person nach Berlin. Für den Besuch von Gemeinschaftsunterbringungen und Schulen bedurfte es einer Aufnahmeuntersuchung sowie dem Ausschluss einer infektiösen Tuberkulose. Wir konnten zeigen, dass ein Screening auf TB bei unbegleiteten minderjährigen Flüchtlingen auch bei großen Flüchtlingszahlen durchführbar ist und dass nicht nur Kinder- und Jugendliche aus Hochinzidenzländern, sondern auch aus Ländern mit niedriger TB-Inzidenz aufgrund der Bedingungen während der Flucht und bei Unterbringung in Massenunterkünften ein hohes Risiko für eine TB-Infektion aufweisen. In unsere Studie wurde bei 301 Kindern und Jugendlichen ein TB-Screening mittels eines IGRAs durchgeführt. Zweiundvierzig (13,9%) der 301 minderjährigen Flüchtlinge zeigten ein positives Ergebnis und erhielten weitere Diagnostik. Bei zwei Patient*innen konnte im Röntgenthorax eine Lungen-TB diagnostiziert werden, bei 38 wurde die Diagnose einer LTBI gestellt und 2 konnten nicht nachverfolgt werden. Drei Patient*innen zeigten zusätzlich eine aktive Hepatitis B. Die Patient*innen mit LTBI erhielten eine dreimonatige Chemoprävention mit RMP und INH. Die Therapie wurde insgesamt gut vertragen, die häufigste Nebenwirkung waren transiente gastrointestinale Beschwerden. Neunundzwanzig Patient*innen komplettierten die Therapie, 9 Patient*innen waren „lost to follow-up“. Dies zeigt die Herausforderungen der Versorgung einer Patientengruppe, die häufig nur temporär in einer Gemeinschaftsunterkunft untergebracht ist. Da eine LTBI keine meldepflichtige Erkrankung ist, ist eine Nachverfolgung der betroffenen Kinder und Jugendlichen zusätzlich erschwert. Das bedeutet auch, dass das Risiko einer nicht adäquat durchgeführten Therapie und damit das Erkrankungsrisiko in dieser Gruppe erhöht ist.

PLOS ONE

RESEARCH ARTICLE

Screening and treatment for tuberculosis in a cohort of unaccompanied minor refugees in Berlin, Germany

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Abstract

Introduction

In 2015, 4062 unaccompanied minor refugees were registered in Berlin, Germany. According to national policies, basic clinical examination and tuberculosis (TB) screening is a prerequisite to admission to permanent accommodation and schooling for every refugee. This article evaluates the use of an interferon-γ-release-assay (IGRA) during the initial examination and TB screening of 970 unaccompanied minor refugees.

Results

IGRA test were obtained during TB screening for 301 (31.0%) of 970 adolescents not previously screened for TB. Positive IGRA results were obtained in 13.9% (42/301). Most of the 42 IGRA-positive refugees originated from Afghanistan or Syria (n?20 and 10 respectively). Two IGRA-positive adolescents were lost to follow-up, 2 were diagnosed with TB and the remaining 38 diagnosed with latent TB infection (LTBI). Demographic features of the 40 patients with positive IGRA result were as follows: 39 male, median age 16.8 years (IQR 16.0–17.2y), none meeting underweight criteria (median BMI 21.3kg/m^2). On initial chest X-ray 2/40 participants had signs of active TB, while in 38 active disease was excluded and the diagnosis of latent TB infection (LTBI) made. Active hepatitis B-co-infection was diagnosed in 3/38 patients. All patients with LTBI received Isoniazid and Rifampicin for 3 months without occurrence of severe adverse events. The most frequently observed side effect was transient upper abdominal pain (n = 5). Asymptomatic elevation of liver transaminases was seen in 2 patients. 29 patients completed treatment with no signs of TB disease at the end of chemoprevention and 9 were lost to follow up.

Conclusion

Screening for TB infection in minor refugees was feasible in our setting with a relatively high rate of TB infection detected. Chemopreventive treatment was tolerated well regardless of

Competing interests: Labor Berlin, Charité Vivantes GmbH is affiliated with Charité Universitätsmedizin and belongs to the public sector. In general, all samples of the Charité Universitätsmedizin are analyzed in this laboratory and accordingly the IGRA-tests of the participants of our study. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

underlying hepatitis-B-status. Minor refugees migrating to Germany should be screened for TB infection, instead of TB disease only, regardless of the background TB incidence.

Introduction

In 2015, around 1.1 million refugees were registered in Germany with estimated 40,000–60,000 unaccompanied minor refugees. Most of the unaccompanied minors originated from Afghanistan (34%), Syria (31%), Iraq (8.4%), Eritrea (8.1%) and Somalia (4.5%) [1]. In the city of Berlin, 4062 minor refugees were registered in 2015.

According to German national policies, every refugee has to undergo basic clinical examination and infectious tuberculosis (TB) is to be ruled out as soon as possible after entry to the country. This is a prerequisite to admission to permanent accommodation and schooling. Besides, vaccinations against tetanus, diphtheria, pertussis, poliomyelitis, mumps, measles and rubella are offered in case of incomplete or unknown immunization status.

TB screening is based on a chest X-ray in persons older than 15 years of age. In those younger than 15 years of age, making about 25% of all refugees, an interferon-γ-release-assay (IGRA) or the tuberculin skin test (TST) have been proposed for screening purposes [2] [3]. In case of symptoms of TB or a positive TST or IGRA a chest radiograph is obtained also in those being under 15 years of age.

A previous study informs about screening for infectious diseases except tuberculosis in minor refugees [4]. But regarding the burden of TB infection and TB disease, a substantial lack of knowledge exists for this cohort.

In many unaccompanied minors no TB screening or vaccinations were performed upon arrival to Germany, impeding schooling and further integration, because special initial acceptance facilities, so-called clearing offices, for unaccompanied minor refugees had to be established. Additionally, there was uncertainty on how to perform medical procedures in lack of a legal guardian.

In an action campaign in January 2016, initiated by the Charité—Universitätsmedizin Berlin ("Charité hilft"), unaccompanied refugees <18 years of age residing in Berlin were offered initial basic clinical examination, TB screening as well as the vaccinations mentioned above. For logistical reasons, an IGRA (QuantiFERON®-TB Gold In-Tube) was performed in those not having received TB screening (either TST, IGRA or chest-X-ray) before regardless of age.

This article provides information on the initial tuberculosis screening of unaccompanied minor refugees, focusing on those with positive IGRA results. Participants diagnosed with TB or latent tuberculosis infection (LTBI) received treatment according to national standard of care and were followed up prospectively. This data also adds to the limited body of evidence on chemopreventive TB treatment in adolescents, an age-group being considered as being more susceptible to drug induced hepatotoxicity compared to younger children [5, 6].

Methods

Local authorities as well as several local charity organizations caring for unaccompanied minor refugees were contacted and informed about the screening campaign and asked to inform the refugees they care for. All minors participating received information on the screening and vaccination procedures in their mother tongue beforehand and were asked for written consent. Additionally, a questionnaire on the medical history including information on previous TB screening was asked to be filled in. Inclusion criteria were children and adolescents

younger than 18 years of age with no signs of acute illness. In case of acute illness, the person was referred to a local medical service. At the day of the screening, interpreters of all languages mainly spoken by the refugees were available.

Participants were interrogated for any symptoms or complains and received a basic clinical examination. In case no TB screening had been performed, blood for the IGRA-test was taken by venipuncture. Vaccinations were offered if evidence of a complete immunization status was missing.

Blood samples for IGRA tests were transferred to the laboratory at site within two hours. Participants with a positive IGRA test (IFN-$\gamma > 0.35$ IU/mL) were followed up in the paediatric infectious disease clinic of the Charité University medicine. A chest X-ray was performed. In the absence of signs for active TB, the diagnosis of LTBI was made and chemopreventive treatment recommended. According to national guidelines, 3 months of isoniazid (INH) in combination with rifampicin (RMP) are recommended for chemopreventive therapy if no drug resistance was suspected. Because the index cases were not known in our cohort, susceptibility to INH and RMP was assumed and treatment started accordingly. In case of signs for TB disease, further diagnostic procedures according to national standards were performed and TB treatment initiated accordingly.

Before initiation of chemopreventive treatment, a baseline laboratory examination including whole blood cell count, liver transaminases, alkaline phosphatase, creatinine, uric acid and hepatitis B and C serology was performed. Patients were followed up clinically and laboratory tests were repeated after 2 and 6 weeks. At each follow-up visit, adherence was checked by either interrogation, pill count or inspection of urine for red-orange-coloring (due to RMP intake). Before chemoprevention was stopped and if possible one year after the end of chemoprevention, further chest X-rays were performed to exclude development of TB disease due to non-adherence, drug resistance or treatment failure.

Results

Nine-hundred-seventy adolescents (median age 16.8 years, range 13.6–17.1years) participated in the screening campaign. Of 970 participants, 301 had not been screened for TB. The leading countries of origin of these participants were Afghanistan (125/301; 41.5%), Syria (69/301; 22.9%), Lebanon and Iran (both 14/301, 4.7%). 26 adolescents (8.6%) refused to indicate their country of origin. An IGRA-test was performed for TB screening, with 42 (13.9%) tested positive (see Table 1 for distribution according to country). Two of these adolescents were lost to follow-up, the remaining 40 were seen at the paediatric infectious disease clinic Charité University Medicine, Berlin.

Demographic features of this cohort were as follows: 39 male, 1 female, median age 16.8 years (IQR 16.0–17.2y), median weight 62.5kg (IQR 58.4–66.5), median BMI 21.3kg/m^2 (IQR 20.3–22.6kg/m^2). Therefore, none of the participants met underweight criteria [7]. Positive IGRA-test results varied from 0.39–15.46 IU/ml (median 3.39IU/ml). In the adolescent with an IGRA-result of 0.39IU/ml a repeated test one month later showed a result of 1.26IU/ml.

The initial chest X-ray showed signs of intrathoracic TB in 2 cases (one from Syria, one from Afghanistan) being transferred to a paediatric clinic for further diagnostic work-up and treatment. One of these adolescents reported weight loss and fatigue, but both did not have symptoms like persistent cough or night sweats. One patient had hilar lymphnode TB and the other pulmonary TB, both without detection of M. tuberculosis in sputum. In another adolescent with positive IGRA-test, a small pleural effusion was suspected that cleared without treatment. A further patient reported of cough for more than 8 days and night sweats without weight loss, but had a normal chest X-ray.

Table 1. Country of origin of participants according to WHO world regions[37], number of participants receiving interferon-γ-release-assay (IGRA) -testing (n = 301) and numbers of positive (IGRA) test results (n = 42) according to country of origin.

World region of origin	*Number participants*	*IGRA test positive/ number tested per world region*	*Country of origin*	*IGRA test positive/ number tested per country*
African Region	59	3/23		
			Benin	1/1
			Chad	0/3
			Eritrea	0/2
			Gambia	2/8
			Ghana	0/1
			Guinea	0/2
			Guinea-Buissau	0/1
			Kenya	0/2
			Mali	0/2
			Somalia	0/1
South-East Asia Region	12	2/7		
			Bangladesh	1/4
			India	1/2
			Vietnam	0/1
Eastern Mediterranean Region	825	32/237		
			Afghanistan	19/125
			Iran	0/14
			Iraq	1/5
			Kurdistan	0/1
			Lebanon	1/14
			Libya	1/1
			Morocco	1/2
			Pakistan	0/5
			Syria	9/69
			Tunisia	0/1
European Region	17	1/8		
			Albania	0/1
			Moldova	0/1
			Palestine	0/4
			Turkey	0/1
			Turkmenistan	1/1
Unknown	57	4/26		4/26
Total	**970**	**42/301**		**42/301**

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In 38 adolescents, the diagnosis of LTBI was made and chemoprevention with 3 months INH/RMP recommended. Four patients were seen at the initial visit only. Of 29 patients seen at 3 months before stopping treatment, 10 had been seen for follow up visits while being on chemopreventive therapy once and 19 twice, respectively. Four patients were seen during treatment, but lost to follow up at the 12 weeks visit. Main reason for lost to follow up was relocation to another city. At the three months visit, a chest X-ray was taken again before chemoprevention was stopped. Twenty-eight of 29 chest X-rays were reported to be normal. Nine patients received a chest x-ray one year after completion of chemoprevention and none developed TB. In one patient, very small (<1 cm) opacifications with calcifications in the right

upper lobe were detected in the follow-up chest X-rays that had been missed in the initial report. In this patient, the diagnosis of previous TB was made retrospectively.

Testing for hepatitis B and C was performed in 38/38 cases, and active hepatitis B infection was diagnosed in 3 cases. Initial viral load was 178, 105 and >70 000 000 HBV-DNA IE/ml, respectively. There was no case of hepatitis C. Baseline liver transaminases were slightly elevated (< 3times upper limit) in 3 cases of which 1 had active hepatitis B. This patient had a viral load >70.000,000IE/ml and was started on treatment with entecavir at the end of chemopreventive TB treatment. Anaemia was found at baseline in 3 patients (minimal Hb 9.0g/dl); no further abnormalities were noted.

Non-adherence was suspected in 10 adolescents during treatment followed by counselling again. At the end of treatment non-adherence was only suspected in 1/29 patients. No severe adverse events occurred and treatment had not to be stopped due to side effects in any case. Transient upper abdominal pain was reported in 5 cases. One patient with chronic hepatitis B had permanent gastric discomfort. One patient complained about alopecia. Asymptomatic elevation of liver transaminases above 3 times upper normal limit (but <5times upper normal limit) occurred in two patients (one chronic hepatitis B co-infection). Patients were monitored for signs of increased hepatotoxicity, but therapy could be continued until completion of 3 months therapy. Transaminases normalized or decreased with cessation of treatment with INH and RMP.

Discussion

Concordant with official German refugee reports, the majority of our cohort originated from Afghanistan and Syria. According to WHO country reports, Afghanistan has a TB incidence of 189/100.000, while Syria is considered a low TB burden country with an estimated incidence of 19/100.000 [8]. For comparison, TB incidence was 7.2/100.000 in Germany in 2016 [9].

Two patients of our cohort with a positive IGRA (n = 42) had radiographic signs of active TB. Because persons with acute illness were excluded from our campaign, the true burden of TB in refugee minors might have been underestimated. Comparison with other studies is challenging because of the large diversity of policies on TB and TB infection screening in European countries [10]. In some European countries (e.g. Netherlands, Sweden, Spain) TB screening is restricted to asylum seekers originating from countries with a TB-incidence of more than 40-100/100 000, while others aim to screen all asylum seekers (e.g. Belgium, Germany) regardless of TB incidence in home countries according to WHO estimates [10]. In Switzerland, symptom triage screening is performed and only those classified as being at risk for TB are screened further using a chest X-ray (www.tb-screen.ch). Besides the targeted population, the target of TB screening itself varies from country to country. Sometimes, a TST or an IGRA is performed to detect tuberculosis infection (mainly in children or younger adults) while other focus on tuberculosis disease and primarily only a chest x-ray is taken.

In a study on a large cohort (n = 2936) of unaccompanied minors seeking asylum in Sweden in 2015, Bennet et al. reported numbers of TB disease of 500-3400/100,000 [11]. According to Swedish policy, screening is restricted to migrants from countries with a TB burden of more than 100/100,000 or if the screening doctor found other risk factors for TB. Therefore, 82% of the Swedish cohort originated from high burden countries (HBC), while in our study as well as in a further German pediatric study, migrants from HBC, besides Afghanistan, only form a small minority [12].

These higher numbers of TB found in the study by Bennet et al. as well as in our study are likely attributable to a high risk for both, TB infection and progression to disease, under conditions of conflict or humanitarian crisis in the country of origin as well as during transit to

Europe [13]. Depending on many factors like background TB incidence, access to health care, nutrition, overcrowding, transit time, migration route and others, estimates of TB incidence can often dramatically exceed TB incidence of the country of origin [13] [14]. Transit time was asked for in all refugee minors of our cohort, but responds were often very imprecise or refused.

In our study, both adolescents with TB disease would have been missed in a symptom based approach. In a TB screening exclusively performed in refugees from HBC, only the patient from Afghanistan, but not the one from Syria would have been detected. In Finnish screening guidelines, the increased risk for TB in migrants from conflict areas has been taken into account and all migrants from Syria and Iraq are screened with chest X-ray while otherwise screening is restricted to countries with a TB incidence of more than 40/100 000 [10].

All patients in our study diagnosed with LTBI received a combination therapy with INH and RMP for 3 months. The medication was tolerated fairly well, no major side effects were observed. Hepatotoxicity is the most serious adverse effect related to INH with rare reports on acute liver failure even during chemopreventive therapy [15]. In previous studies on children treated with INH for LTBI, asymptomatic elevated liver enzymes were found in 5–10%, with a higher incidence in adolescents compared to adults [5, 16–20]. Besides INH-dose, disease severity, slow-acetylator status and co-medication with RMP have been identified as risk factors for hepatotoxicity [16]. Based on our experience in a German pediatric cohort, chemopreventive therapy with INH and RMP is very well tolerated [21].

The impact of chronic hepatitis B infection on antituberculotic drug-induced liver injury is discussed controversially and has been inconsistently identified as a risk factor for hepatotoxicity [22, 23]. Gray et al. identified abnormal baseline liver function tests to be associated with INH-associated hepatotoxicity in chemopreventive therapy, but no information on the underlying cause of elevated liver enzymes is provided [24]. Increase of liver transaminases above 3 times above the normal upper range was noted in two patients, one being a patient with active hepatitis B.

The adolescents of our study were accommodated in Berlin only temporarily, facing relocation at any time. These circumstances are not only reflected in the relatively high number of persons (n = 9/38) lost to follow-up at the end of chemopreventive treatment but also in the number of adolescents in whom non-adherence during chemopreventive therapy (n = 10) was suspected. However, following counselling, non-adherence at the end of chemoprevention was only suspected in one patient.

Treating LTBI is a cornerstone for elimination of TB in low incidence countries and growing evidence on tolerability and efficacy of chemopreventive treatment exists [25]. Numerous studies have shown that a majority of incident TB cases among migrants arise through the reactivation of LTBI probably acquired outside the host country. Epidemiological evidence also shows that progression from LTBI to tuberculosis disease usually occurs within the first two years after arrival [26, 27]. In a recent publication, results of 17 years LTBI screening in England among non-UK born individuals were evaluated, demonstrating a strong association between no chemoprophylaxis and developing TB disease [28]. Therefore, screening programs only aiming to identify adults with active TB neglect addressing the reservoir of tuberculosis and the risk of transmission of TB within refugee centers and to the resident population [29]. Concerns have arisen about the feasibility of LTBI screening in all pediatric refugees. While screening for TB infection was feasible in our setting, some patients were lost to follow up during chemopreventive treatment. In Germany, it is standard of care to perform a chest X-ray after completion of chemopreventive treatment. The risk of TB disease following treatment with INH and RMP has been reported to be approximately 4% and equal to treatment with INH monotherapy [30]. If a clinical follow-up or repetition of chest X-rays is the most

appropriate way to monitor patient for the development of active TB is beyond the scope of the current study. Recently, data is emerging showing equal efficacy and safety of 3-4months RMP alone versus 6–9 months of INH with better adherence in the shorter RMP regimen [31]. With this data in mind, adding INH for chemoprevention might add to the risk for hepatoxicity without improving efficacy and has come under scrutiny. Nevertheless, there is no clear evidence demonstrating increased hepatotoxicity rates in children receiving combination therapy. At the time of the study, combination of INH and RMP has been standard therapy in Germany and endorsed by WHO LTBI treatment guidelines [32]

Any screening program faces screening in a high number of migrants to detect those who actually are infected with tuberculosis or have the disease [33]. For LTBI screening, the body of evidence for implementation, impact and cost-effectiveness as predicted in mathematical models is still limited and setting-specific [34, 35]. However, evidence exists for cost-effectiveness of school-based tuberculosis screening programs for children migrating to low-incidence countries [36]. For the greatest individual and public health benefits, more emphasis must be placed on strategies not only to ensure screening but also to facilitate treatment completion.

In summary, we report on a cohort of minor refugees originating from high but also from low TB burden countries with a high incidence of TB and LTBI. Screening for TB infection instead of TB disease was feasible and chemopreventive treatment with 3 months of INH and RMP tolerated well regardless of underlying hepatitis B status. Minor refugees migrating to Germany should be screened for TB infection, instead of TB disease only regardless of the background TB incidence. For the greatest individual and public health benefits, more emphasis must be placed on strategies not only to ensure screening but also to facilitate treatment completion.

Supporting information

S1 File. Questionnaire TB screening.
(PDF)

S1 Dataset. Minimal data set.
(XLSX)

Author Contributions

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Um das Ziel einer (Prä-)Elimination der Tuberkulose in Niedriginzidenzländern zu erreichen, ist nicht nur die Identifikation von Risikogruppen, sondern auch die Behandlung der LTBI sowie die optimierte Therapie der manifesten TB von essentieller Bedeutung. Bis zum Jahr 2017 lagen keine nationalen Leitlinien zur Diagnostik und Therapie von Kindern und Jugendlichen mit einer LTBI und/oder TB vor. Im Rahmen der folgenden Studie erfolgte eine Befragung zur Diagnostik und Therapie der LTBI unter pädiatrischen Pneumologen und Infektiologen in Deutschland, Österreich und der Schweiz, um Optimierungsmöglichkeiten zu identifizieren, die bei der Erstellung aktueller Leitlinien und deren Verbreitung berücksichtigt werden können.

3.2 Diagnostik und Therapie der latenten Tuberkuloseinfektion bei Kindern und Jugendlichen in Deutschland, Österreich und der Schweiz

Ulrich von Both, Philipp Gerlach, Nicole Ritz, Matthias Bogy, Folke Brinkmann, ***Stephanie Thee****. Management of childhood and adolescent latent tuberculous infection (LTBI) in Germany, Austria and Switzerland. PLoS ONE 16(5): e0250387. https:// doi.org/10.1371/journal.pone.0250387*

An unserer Erhebungsstudie nahmen 191 pädiatrische Pneumologen und Infektiologen aus Deutschland, Österreich und der Schweiz teil, wobei 173 Fragebögen in der finalen Analyse ausgewertet werden konnten. Sechzig Prozent der Befragten kamen aus Deutschland, 28% aus der Schweiz und 12% aus Österreich. Weniger als 10% der Befragten gab an, mehr als 50 Kinder/Jugendliche pro Jahr auf eine TB hin zu untersuchen. Es wurde des Weiteren angegeben, dass ein Großteil der Patient*innen einen Migrationshintergrund hatte. Zur Diagnostik der LTBI verwendeten 86% der Befragten einen THT und 88% einen IGRA-Test. Bei Kindern unter 5 Jahren gaben 53% an, eine unterschiedliche Vorgehensweise zu wählen, wobei hier meist der THT, ein IGRA-Test sowie ein Röntgenbild kombiniert verwendet wurden. Achtundsechzig Prozent verwendeten als Chemoprävention bei LTBI eine INH-Monotherapie über 9 (62%) oder 6 Monate (6%), 31% eine Kombinationstherapie aus INH und RMP. Bei 22% der Befragten lagen die verwendeten Dosierungen von INH und RMP unterhalt der aktuellen Dosisempfehlungen. Mehr als 90% gaben an, laborchemische Blutwertkontrollen vor oder während der LTBI-Therapie durchzuführen, 51% ein Röntgenbild am Ende der Therapie.
Wir konnten eine deutliche Heterogenität im Management der LTBI in Deutschland, Österreich und der Schweiz sowie eine häufige Unterdosierung der antituberkulösen

Medikamente zeigen. Regelmäßige und einfach zugängliche Fortbildungsveranstaltungen und das Vorhandensein aktueller Leitlinien sind essentiell, um das Wissen zur Diagnostik und Therapie dieser Erkrankung und die Qualität der Versorgung von Kindern und Jugendlichen in Ländern mit niedriger TB-Inzidenz zu verbessern.

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RESEARCH ARTICLE

Management of childhood and adolescent latent tuberculous infection (LTBI) in Germany, Austria and Switzerland

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Abstract

Background

Majority of active tuberculosis (TB) cases in children in low-incidence countries are due to rapid progression of infection (latent TB infection (LTBI)) to disease. We aimed to assess common practice for managing paediatric LTBI in Austria, Germany and Switzerland prior to the publication of the first joint national guideline for paediatric TB in 2017.

Methods

Online-based survey amongst pediatricians, practitioners and staff working in the public health sector between July and November 2017. Data analysis was conducted using IBM SPSS.

Results

A total of 191 individuals participated in the survey with 173 questionnaires included for final analysis. Twelve percent of respondents were from Austria, 60% from Germany and 28% from Switzerland. Proportion of children with LTBI and migrant background was estimated by the respondents to be >50% by 58%. Tuberculin skin test (TST) and interferon-γ-release-assay (IGRA), particularly Quantiferon-gold-test, were reported to be used in 86% and 88%, respectively. In children > 5 years with a positive TST or IGRA a chest x-ray was commonly reported to be performed (28%). Fifty-three percent reported to take a different diagnostic approach in children $\leq$ 5 years, mainly combining TST, IGRA and chest x-ray for initial testing (31%). Sixty-eight percent reported to prescribe isoniazid-monotherapy: for 9 (62%), or 6 months (6%), 31% reported to prescribe combination therapy of isoniazid and rifampicin. Dosing of isoniazid and rifampicin below current recommendations was reported by up to

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22% of respondents. Blood-sampling before/during LTBI treatment was reported in >90% of respondents, performing a chest-X-ray at the end of treatment by 51%.

Conclusion

This survey showed reported heterogeneity in the management of paediatric LTBI. Thus, regular and easily accessible educational activities and national up-to-date guidelines are key to ensure awareness and quality of care for children and adolescents with LTBI in low-incidence countries.

Introduction

In 2014, the World Health Organization (WHO) released an action framework to eliminate tuberculosis (TB) in low incidence countries [1] as part of the global "Stop TB" strategy. This action framework aims to progress from <100 cases per 1 million inhabitants towards "pre-elimination" of TB (defined as <10 TB cases per million) until 2035 [1]. Because in low-incidence countries most cases of active TB in children are due to rapid progression of latent TB infection (LTBI) to TB disease, prevention strategies must focus on early screening for and treatment of LTBI. This is particularly true for migrant children who recently arrived from high-TB-endemic regions [2, 3]. Following infection with *Mycobacterium tuberculosis (M. tb)*., there is a general life-time risk of 5–10% to develop TB [4, 5]. In children and adolescents however, the risk to develop TB disease following infection is far greater and estimated to be 15% within 5 years up to 33% within one year depending on age and study setting [6]. The detection of LTBI relies on immune-based diagnostics: either the tuberculin skin-test (TST) or an interferon-γ-release assay (IGRA). While IGRA testing has demonstrated a greater specificity than TST, its sensitivity in children younger than 5 years of age is less established [7]. In order to exclude pulmonary TB, a chest x-ray is routinely recommended even in asymptomatic children [8]. Once, TB disease is excluded, highly LTBI treatment regimens exist to prevent progression from infection to TB disease. These regimens include isoniazid (INH) for 6–9 months, rifampicin (RMP) for 4months or a combination therapy with INH and RMP for 3 months [9, 10]. Currently recommended daily doses in TB therapy for INH and RMP are INH 10 mg/kg and RMP 15 mg/kg bodyweight, respectively [11] and were increased from previous guidelines from INH 5mg/kg and RMP 10mg/kg following pharmacokinetic studies in children [12–16]

Austria, Germany and Switzerland represent a population of 100 million people in central Europe with figures of 8.9, 82.6, and 8.5 million, respectively. All three countries are classified as low-TB-incidence countries with an incidence of 5.0–5.8 per 100,000 in 2018/2019 [17–19]. According to national infection protection acts, refugees as well as contacts of persons with infectious tuberculosis are to be investigated for tuberculosis [2, 20]. Only by 2017, first common guidelines on management of paediatric TB including LTBI were published for these three countries [21]. These guidelines emphasize that "intention to test is intention to treat" and any positive immunological test (TST and/or IGRA), should lead to initiation of treatment for LTBI or investigation and treatment for TB disease [21]. In 2016, there was an European-wide shortage of PPD RT23 SSI tuberculin strain (manufactured by the Statens Serum Institut, Copenhagen, Denmark), possibly influencing diagnostic procedures [22]. Because of the increased risk for progression to disease [4, 6], diagnostic procedures and management of LTBI might differ in children younger than 5 years-of age compared to older children.

This study aims to describe clinical practice for LTBI in the paediatric population of Austria, Germany and Switzerland and to add important real-life data to the limited body of evidence on diagnostic procedures, therapy and management in children of different age-groups with LTBI from low-incidence countries.

Methods

Members of established paediatric pneumology and infectious diseases societies including the Austrian Pediatric Society (ÖGKJ), the Germany-based Society for Pediatric Pneumology (GPP), the German Society for Pediatric Infectious Diseases (DGPI), the Swiss Society for Pediatric Pneumology (SGPP-SSPP) and the Pediatric Infectious Disease Group of Switzerland (PIGS) as well as members of the responsible public health department were invited via email to participate in the survey. In Switzerland, cantonal representatives from the Swiss Lung Association (Lungenliga Schweiz) and university hospitals were contacted for personal interviews and to fill in the survey. The survey consisted of 44 questions divided into 6 subsections and was available in German, English and French (the English version of the document is available, see S1 Appendix).

Data were collected between July 14th until November 15th 2017 via a web-based tool (surveymonkey) creating a standardized dataset for each case or a paper-based questionnaire. It was made sure that no respondent filled in the questionnaire more than once using IP-lock. Information on the affiliated institution, the diagnostic methods including procedures to exclude TB disease, treatment regimens for LTBI and follow-up was collected. This survey sought responses from healthcare professionals via collaborative networks and societies and did not contain any patient identifiable data; ethics approval was therefore not required. Data collected consisted of categorical variables and are presented as frequencies (number and percentage of patients). Data analysis was conducted with IBM SPSS version 25.

Results

Study population

A total of 191 individuals took part in the survey of which 18 data sets were exclude because of substantially incomplete data. One-hundred-seventy-three data sets were included in the final analysis of which 104/173 (60.1%) respondents were from Germany, 49/173 (28.3%) from Switzerland and 20/173 (11.6%) from Austria. Number of respondents per federal state ("*Bundesland*" in Germany and Austria and "*Kanton*" in Switzerland) and institutional affiliations of the respondents are depicted in Fig 1 and Table 1, respectively. Seventy-three of 173 (42.2%) respondents reported to evaluate less than 10 children for LTBI/TB each year, 83/173 (48.0%) 10–50 children, and 16/173 (9.3%) more than 50 children per year; one respondent provided no data (0.6%). The respondents estimated the proportion of migrant children to be >80% in 47/173 (27.2%), 50–80% in 54/173 (31.2%), 20–50% in 23/173 (13.3%) and <20% in 10/173 (5.8%), respectively. One respondent (0.6%) reported none of the children being migrants and in 38/173 (22.0%) no information was provided.

Immunodiagnostic testing

When testing for LTBI, 149/173 (86.1%) reported to perform a TST, 152/173 (87.9%) an IGRA-test. Quantiferon gold (Plus) was reported to be the IGRA-test used by 118/173 (68.2%), T-SPOT.TB by 18/173 (10.4%) and both IGRA-tests equally by 19/173 (11.0%); for 18/173 (10.4%) respondents this data were not provided. Choice of IGRA differed between the three countries: T-SPOT.TB alone was used by 2/20 (10.0%) in Austria, by 9/104 (8.7%) respondents

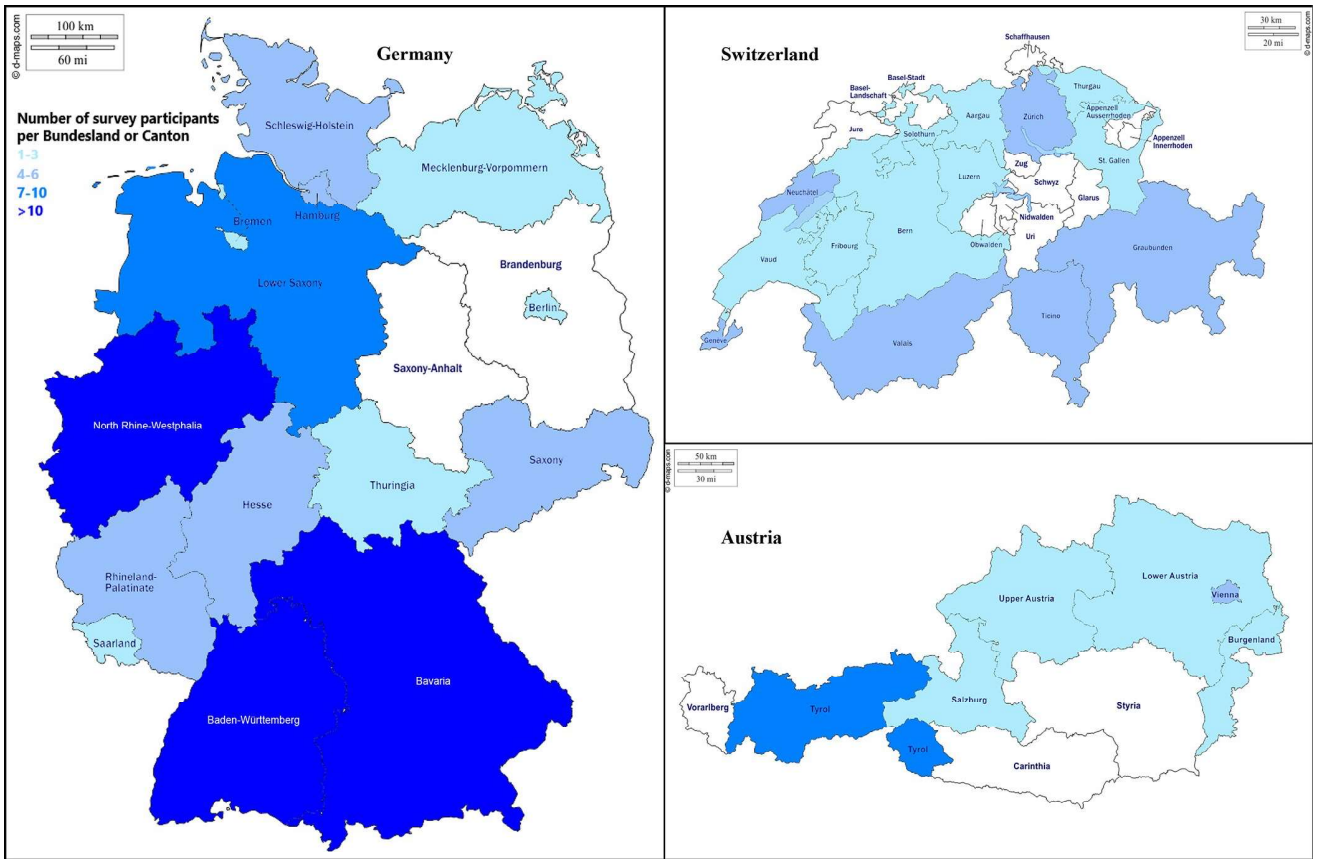

Fig 1. Number of survey respondents per federal state or canton, respectively. Reprinted under a CC BY license, with permission from [Daniel Dalet], original copyright [2020].

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in Germany, and 7/49 (14.3%) in Switzerland while both IGRA tests were used by 9/104 (8.7%) in Germany, 4/20 (20.0%) in Austria and 6/49 (12.2%) in Switzerland, respectively.

Ninety-one/173 (52.6%) of the respondents reported to have been affected by the 2016 shortage of PPD RT 23 SSI tuberculin. In 18/91 (19.8%) cases an alternative tuberculin was used. Three respondents from Germany (3.3%) stated to rather use TST in younger children, but were forced to switch to IGRA testing due to this PPD RT 23 SSI shortage.

Radiology

For the diagnosis of LTBI in children > 5 years of age, the most common procedure reported to exclude TB-disease (48/173, 27.7%) was performing a chest-x-ray in case of an either positive IGRA or TST.

Table 1. Institutional and geographical background of survey respondents.

Institution / Country	University hospital	Central hospital / teaching hospital	District general hospital	Private hospital	Private practice	Shared doctor's office or medical care center	Public health service	Total
Austria	2	7	3	0	0	0	8	20
Germany	24	27	7	4	11	1	30	104
Switzerland	14	14	1	1	5	0	14	49
Total	40	48	11	5	16	1	52	173

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Table 2. Reported diagnostics for LTBI in children older and younger than 5 years of age.

Procedure	> 5 years of age	≤5 years of age
TST only	5 (2.9%)	3 (1.7%)
IGRA-test only	7 (4.0%)	2 (1.2%)
TST + IGRA	9 (5.2%)	6 (3.5%)
TST + chest-x-ray	5 (2.9%)	41 (23.7%)
IGRA + chest-x-ray	29 (16.8%)	5 (2.9%)
TST + IGRA + chest-x-ray	37 (21.4%)	54 (31.2%)
Chest-x-ray only if IGRA or TST positive	48 (27.7%)	22 (11.7%)
Other	13 (7.5%)	18 (10.4%)
Missing/unknown	20 (11.6%)	21 (12.2%)

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Ninety-three/173 (53.8%) respondents reported to choose a different approach for children ≤5 years of age. One hundred/173 (57.8%) respondents reported to include a chest x-ray in the initial diagnostic work-up for LTBI in children ≤5 years of age compared to 71/173 (41.0%) in children > 5 years of age, respectively. Table 2 depicts diagnostic procedures and their frequencies in both age groups.

Treatment

For LTBI treatment, information on treatment was missing in 29/173 (16.7%) or unknown in 5/173 (2.9%) respondents. In the remaining 139 answers, 94/139 (67.6%) reported to prescribe INH monotherapy: 87/139 (62.6%) used INH monotherapy as their first choice, whereby in one respondent a different approach was chosen for migrant children and in another respondent INH monotherapy was only prescribed for children ≤ 5 years of age (and combination of INH and RMP in children >5years); 4/139 (2.8%) stated to equally use INH or RMP and 3/139 (2.2%) either INH or a combination of INH and RMP. Two/139 (1.4%) used RMP monotherapy (both for four months), 43/139 (30.9%) a combination of INH and RMP. Table 3 describes duration and dose of commonly used anti-TB agents. Of note, LTBI treatment was exclusively prescribed as daily therapy with no intermittent regimens reported. For INH, 9/94 (9.6%) respondents reported doses below the recommended range, and 12/54 (22.2%) for RMP. INH monotherapy was reported to be prescribed by respondents from Germany in 52/76 (68,4%), by respondents from Austria in 8/18 (44,4%) and from Switzerland in 27/45 (60,0%), while for combination therapy of INH and RMP it was 22/76 (28.9%), 6/18 (33.3%) and 15/45 (33.3%), respectively.

Monitoring and follow-up during treatment

Information on monitoring of compliance was available in 124/173 (71.7%) respondents. Ninety-six/124 (77.4%) reported to check the patient's compliance during therapy by verbal interrogation at each patient's visit. Visual inspection of urine color in patients on RMP was stated to be routinely done by 10/54 (18.5%). Directly observed therapy was reported to be arranged by 8/124 (6.4%).

Routine blood sampling was reported to be done in 166/173 (96.0%) before and in 163/173 (94.2%) during treatment. Frequency of requested specific analysis prior and during treatment were as follows: liver function tests 111/116 (95.7%) and 104/163 (63.8%), full blood count 103/166 (62.0%) and 92/163 (56.4%), creatinine 68/166 (41.0%) and 47/163 (28.9%), electrolytes 49/166 (29.5%) and 30/163 (18.4%) and C-reactive protein 39/166 (23.5%) and 9/163 (5.5%), respectively.

Table 3. Reported dose and duration of antituberculosis agents in LTBI treatment.

a)

INH dose		RMP dose	
~5mg/kg/d	9 (9.6%)	**~10mg/kg/d**	12 (22.2%)
~10mg/kg/d	50 (53.2%)	**~15mg/kg/d**	18 (33.3%)
~15mg/kg/d	1 (1.1%)	**>15mg/kg/d**	5 (9.3%)
Other dose*	15 (16.0%)	**Other dose**	0
Missing data	19 (20.2%)	**Missing data**	19 (35.2%)
total	94 (100%)	**total**	54 (100%)

b)

Treatment regimen / duration	INH monotherapy	INH / RMP combination therapy
3 months	7 (7.4%)	19 (39.6%)
4 months	1 (1.1%)	9 (18.8%)
6 months	6 (6.4%)	2 (4.2%)
9 months	58 (61.7%)	1 (2.1%)
Other time-span	2 (2.1%)	2 (4.2%)
No information	20 (21.3%)	15 (31.2%)
total	94 (100%)	48 (100%)

Only response included that that stated to use INH and/or RMP for LTBI treatment.

Only those cases were included, that stated to use INH monotherapy or INH / RMP combination therapy for LTBI treatment.

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Information on follow-up visits during LTBI treatment was available from 118/173 (68.2%) respondents: of these 4/118 (3.4%) reported no routine follow-up to be arranged; 14/118 (11.9%) only at the end of treatment, 16/118 (13.6%) reported arranging several follow-up visits. Information on chest x-rays performed at the end of treatment was available from 117 respondents: 63/117 (53.8%) routinely perform a chest-x-ray at the end of LTBI treatment, with 9/12 (75%) from Austria, 49/77 (63.4%) from Germany, and 5/28 (18%) from Switzerland, respectively. One hundred and twenty respondents provided information on routine visits following completion of LTBI treatment: in 32/120 (26.7%) no follow-up visit is reported, in 12/120 (10.0%) only in certain circumstances and 76/120 (63.3%) reported to arrange routine follow-up visits from 2–24 months after completion of LTBI treatment. This differed between Austria, Germany and Switzerland as follows: no follow-up visit in 1/12 (8.3%), 12/79 (15.2%) and 19/29 (65.5%), respectively, only in certain circumstances in 0/12, 7/79 (8.8%) and 5/29 (17.2%), respectively and routine follow-up visits in 11/12 (91.2%), 60/79 (75.9%) and 5/29 (17.2%), respectively.

Exposure to multi-drug-resistant TB

Information on the management in case of exposition to an infectious case with multidrug-resistant (MDR) -TB (drug-sensitivity testing of the index case available) but no signs of infection (IGRA/TST negative) was provided by 115/173 (66.5%) of respondents. In 13/173 (7.5%) is the management was reported as "unknown" and in 45/173 (26.0%) no information was provided. In the remaining 115 respondents, 10/115 (8.7%) reported to always provide prophylactic treatment to the child, 17/115 (14.8%) only if the child was $\leq$ 5 years of age, 13/115 (11.3%) only if risk of infection was high regardless of the age of the child, 35/115 (30.4%) only in children $\leq$ 5 years of age and a high risk for infection, 13/115 (11.3%) reported they would use a "watch and wait" approach, and 27/115 (23.5%) would transfer the child to a TB

specialist. In case of suspected MDR-LTBI, 47/173 (27.2%) respondents did not provide an answer and in 13/173 (7.5%) the management was reported as "unknown". Forty-one/113 (36.3%) reported they would always start LTBI treatment, 12/113 (10.6%) only if the child was < 5 years of age, 3/113 (2.7%) only if the child was ≤ 5 years of age and had an increased risk for infection, 25/113 (22.1%) depending on risk and the patient's/ parent's wish, 30/113 (26.5%) would refer to a TB specialist and 2/113 (1.8%) would not give LTBI treatment at all.

In S2 Appendix information on availability of training on childhood TB is provided.

Discussion

The survey highlights different aspects of paediatric LTBI diagnostics, treatment regimens and follow-up in three high-income, low-TB-incidence countries in central Europe.

The majority of the study respondents evaluate less than 50 children for TB per year bearing the risk of waning expertise for the management of childhood TB in low-incidence countries. Migration from high-TB-incidence countries to Europe continues with migrants being considered at risk for TB [1, 3]. Accordingly, around a third of respondents reported that more than half of children evaluated for TB were migrants that had recently arrived highlighting the relevance of TB in this group [23–25]

Both immunodiagnostic tests, TST or IGRA, are regarded as equal tools in the diagnosis of TB infection [26]. While sensitivity of both tests is comparable, IGRA tests are more specific with less cross-reactivity to non-tuberculous mycobacteria and *Bacillus Calmette Guérin* (BCG) vaccination [27]. In general, Quantiferon Gold tube test was reported to be used more frequently than the T-Spot TB-test, but differences between the countries were noted as practitioners from Switzerland chose T-Spot.TB about twice as often as colleagues from Germany and Austria. Although both IGRA tests are considered interchangeable, some evidence exists that T-Spot.TB might produce a lower rate of indeterminate results in children originating from the African continent and in immunocompromised children [28]. Information on immune status or origin of the children evaluated for TB was not assessed in our survey. However, studies have shown that IGRA tests are less sensitive in younger children with a higher rate of false negative or indeterminate results especially in infants compared to TST [29, 30]. Hence, the TST has been recommended as the standard of care immunodiagnostic test in children < 5 years of age by many experts [7, 31, 32]. Recently, there is growing evidence that new generation IGRA-tests are useful screening tools for TB infection in very young children some experts recommend including IGRAs in the diagnostic work-up even in the youngest age group [21, 33]. The importance of more solid evidence for the use of IGRA-tests in all age groups became particularly evident during the shortage of PPD RT 23 SSI availability in 2016 [22]. More than half of our respondents reported that they were affected by the BCG-shortage, and were forced to use an alternative tuberculin or an IGRA testing instead.

For the exclusion of active TB national and international guidelines recommend performing a chest x-ray in every child and adolescent with a positive TST or IGRA who had been exposed to an infectious TB index case [21, 26, 34]. In view of the reduced sensitivity of immunological tests combined with an increased risk for disease progression in children younger than 5 years of age, chest x-ray is often included in the initial diagnostic work-up in this age group [4]. Accordingly, almost 60% of the respondents reported to routinely perform a chest-x-ray together with an immunological test in younger children, while this approach was practiced in only 40% of children older than 5 years.

INH monotherapy was the first LTBI treatment regimen with proven efficacy against progression from LTBI to TB disease [35]. INH monotherapy is recommended to be given for 9 months -a duration that has shown optimal efficacy with limited hepatoxicity in adults [36].

Shorter regimens using rifamycin-based regimens are increasingly preferred. This includes 3–4 months or RMP monotherapy, 3 months of INH and RMP combination therapy or once-weekly INH and rifapentine for 3 months, the latter not being available in Germany, Austria and Switzerland [37–39].

In our survey, INH monotherapy was the most frequent LTBI treatment reported to prescribed for a duration of 9 months with shorter duration reported in about 15%. Almost twice as many respondents preferred a longer INH monotherapy over a shorter INH-RMP combination therapy. A possible explanation might be concerns about adverse events. Hepatotoxicity is a well-known adverse effect of INH and RMP. The administered dose, TB disease severity, and being an "INH slow-acetylator" have been identified as risk factors for INH- or RIF-associated hepatotoxicity [40, 41]. However, a very low incidence of adverse events and an increased compliance with the shorter combination therapy compared to 9-months INH has been clearly demonstrated in children [42, 43].

Currently recommended daily doses for INH and RMP are INH 10 mg/kg and RMP 15 mg/kg bodyweight, respectively [11] and were increased from previous guidelines from INH 5mg/kg and RMP 10 mg/kg following pharmacokinetic studies in children [12–16]. In the current understanding, LTBI and TB disease are regarded as a continuum of the same disease ranging from asymptomatic infection to clinically active diseases [44, 45]. Therefore, there is no reason to assume that doses for LTBI and TB disease should be different. In our setting, reported dosages were below the recommended range in about a fifth of all respondents.

In order to detect adverse events timely, especially hepatotoxicity, monitoring of liver function during LTBI treatment is advisable. Regular follow-up visits have been recommended for low-incidence countries, while often not being feasible in high-incidence countries [21]. With well-adherent treatment in the context of an infection with a drug-sensitive organism, the risk of progression to disease is low [37, 46].

Nevertheless, in children the index-case or its susceptibility testing might not be available to the clinicians caring for the child or adherence to therapy was less than anticipated bearing an increased risk for treatment failure. Keeping this in mind, regular clinical follow-ups during treatment may increase adherence and detect early LTBI treatment failures. As there is no consensus on the routine use of a chest x-ray at the end of treatment and further follow-up visits with or without additional chest-x-rays after treatment completion, clinical practice is heterogeneous. In addition, follow-up visits especially in groups like refugees might not be feasible for reasons like relocation or return to the home country [2, 47].

In case of exposure to an MDR-strain or MDR-LTBI, the survey confirms further heterogeneity in the management. Numbers of children and adolescents with MDR-TB in Austria, Germany Switzerland are very low. International guidelines differ substantially for children being exposed or infected with MDR-TB with watchful waiting being recommended as well as different treatment regimen with second-line agents with assumed or known susceptibility [48–50]. Studies from South Africa and Micronesia provided evidence for the effectiveness of treatment (MDR-LTBI) and prophylaxis in MDR-TB contacts, with significantly less children progressing to active disease receiving treatment compared to those under clinical supervision only [49, 51]

Our study has limitations: the use of a questionnaire consisting mainly of questions with predefined answers limits the possibility to prescribe individual procedures. This survey was conducted immediately before national guidelines for paediatric TB were released and management of LTBI might have been improved in the meantime [21].

Nevertheless, our data highlights the heterogeneity in diagnostic, treatment and follow-up in paediatric LTBI patients in Austria, Germany and Switzerland. Dosing prescriptions of anti-TB drugs below the current recommended range of recommendations already issued in 2010 [52] in a substantial proportion of respondents is of concern.

Thus, regular and easily accessible educational activities and national up-to-date guidelines are key to ensure awareness and quality of care for children and adolescents with LTBI in low-incidence countries.

Supporting information

S1 Appendix. English version of the survey: Management of childhood and adolescent latent tuberculous infection (LTBI) in Germany, Austria and Switzerland.
(PDF)

S2 Appendix. Availability of training on childhood TB.
(PDF)

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Sowohl die Therapie der LTBI als auch der TB enthält gemäß aktuellen Leitlinien bei fehlendem Hinweis auf einen resistenten Erreger RMP. Trotz der genannten Unterschiede zwischen der TB bei Kindern und Erwachsenen sind die Therapieprinzipien in beiden Gruppen identisch. Es gibt auch keine Hinweise, dass die Dosierung der antituberkulösen Therapie bei einer LTBI anders als bei einer TB erfolgen sollte (Ausnahme schwere Erkrankungsformen, s.u.), da im aktuellen Krankheitsverständnis beide als ein Kontinuum der TB-Manifestation gesehen werden. Die Bestimmung der RMP-Serumspiegel und Optimierung der Dosis bei Kindern hat daher auch in Niedriginzidenzländern eine hohe Relevanz.

3.3 Rifampicin Serumspiegel bei Kindern mit Tuberkulose

Thee S, Detjen A, Wahn U, Magdorf K. Rifampicin serum levels in childhood tuberculosis. Int J Tuberc Lung Dis. 2009 Sep;13(9):1106-11. PMID: 19723399.

Wir konnten in einer ersten pharmakokinetischen Studie an 27 Kindern mit pulmonaler TB im Alter von 2-14 Jahren zeigen, dass Kinder deutlich höhere mg/kg Dosierungen benötigen als Erwachsene. Vor Beginn einer Kombinationstherapie wurden die RMP-Serumspiegel über 24 Stunden nach einer Dosis von RMP 10mg/kg Körpergewicht (KG) an sieben Zeitpunkten gemessen. Nach einer Auswaschphase wurde RMP in Kombination mit EMB gegeben und die RMP-Spiegel erneut gemessen. Der mittlere maximale RMP-Spiegel (C_{max}) nach einer oralen RMP-Dosis von 10mg/kg KG lag zwischen 6,5-7,1µg/ml, in Kombination mit EMB sogar nur zwischen 4,5-5,4µg/ml. Nach einer Standarddosierung von 600mg werden bei Erwachsenen maximale Serumspiegel von 8-24µg/ml erreicht; RMP-Serumspiegel <8µg/ml werden als niedrig, jene <4µg/ml als sehr niedrig erachtet (57, 58). Der Zeitpunkt des höchsten Serumspiegels (T_{max}) lag bei 3,5-4,3 Stunden in allen Altersgruppen. Des Weiteren konnten wir zeigen, dass die „area under the curve“ (AUC) bei jüngeren Kindern niedriger als bei älteren Kindern ist und insgesamt ebenfalls unterhalb der Erwachsenenwerte liegt. Im Jahr 2014 wurden die WHO-Dosisempfehlungen angepasst und eine RMP-Dosis von 15mg/kg KG empfohlen (59).

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Rifampicin serum levels in childhood tuberculosis

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SUMMARY

BACKGROUND: Rifampicin (RMP) is an essential drug in paediatric anti-tuberculosis treatment. The current World Health Organization (WHO) guidelines recommend an oral dosage of 10 (8–12) mg per kg body weight.

OBJECTIVE: To present a study investigating RMP serum levels in children after oral medication of RMP alone and after combination treatment with ethambutol (EMB).

DESIGN: RMP serum levels in children of different age groups were determined after a single oral administration of 10 mg/kg RMP alone as well as after combination with 35 mg/kg EMB.

RESULTS: RMP serum levels were lower than those expected in adults receiving a similar oral dose. RMP serum levels in combination treatment were even lower than in monotherapy.

CONCLUSION: Currently recommended RMP dosages in childhood tuberculosis lead to serum levels lower than those recommended for adults, probably due to different pharmacokinetics and pharmacodynamics in children. In children, it appears to be more valid to calculate RMP dosage on the basis of body surface area rather than body weight, leading to higher dosages especially in younger children.

KEY WORDS: childhood tuberculosis; rifampicin; serum levels; pharmacokinetics

WITH AN ESTIMATED 1 million cases worldwide each year, paediatric tuberculosis (TB) is a serious health problem.[1] Rifampicin (RMP) is an important pillar in modern short-course treatment regimens, and RMP resistance is a disaster for both patients and control programmes.[2] RMP has moderate early bactericidal activity (EBA) against *Mycobacterium tuberculosis*, but in combination with isoniazid (INH), its sterilising ability is unique.[3] RMP is well absorbed from the gastrointestinal tract and distributes extensively throughout the body despite a protein binding of 80%.[4,5] It is metabolised in the liver mainly by acetylation to 25-O-desacetyl-rifampicin, which is also active against *M. tuberculosis* and excreted through the bile and, to a lesser extent, through urine.[4–7] In adults, serum levels of the order of 10 μg/ml occur 2 h after a single oral dose of 600 mg RMP, and are associated with efficacy in clinical studies.[4,5,8,9] As the principles of anti-tuberculosis treatment in children do not differ from those for adults, children should be exposed to the same serum levels.[10] The RMP dosage for children currently recommended by the World Health Organization (WHO) and the American Thoracic Society (ATS) is respectively 10 (8–12) and 10–20 mg per kg bodyweight.[11–13]

Children experience significant changes during growth, not only in height and weight, but also in the relative size of the body compartments as well as in their ability to absorb, metabolise and excrete drugs, leading to pharmacokinetics that differ from those in adults. There is a lack of pharmacokinetic data on anti-tuberculosis drugs in children and fundamental uncertainties about age-appropriate RMP dosage.[14]

A study in children investigating RMP serum levels performed in 1973 at the Department of Paediatric Pneumology and Allergology, Chest Hospital Heckeshorn, Berlin, Germany, was published only nationally at the time.[15] These findings were never made accessible to the international medical community, and they are thus presented here.

RMP serum levels were measured in children of different age groups after oral medication with RMP alone and in combination with ethambutol (EMB). EMB pharmacokinetics were also studied, and the data on EMB were published previously.[16]

MATERIALS AND METHODS

Previously untreated children diagnosed with pulmonary TB at the Department of Paediatric Pneumology

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and Allergology, Chest Hospital Heckeshorn, Berlin, Germany, were included in the study in 1973. Twenty-seven children aged between 2 and 14 years were enrolled in the study, which was approved by the ethics committee of the Free University Berlin. Parents gave informed written consent for participation. Serum levels were studied after the first dose of RMP was given. After completion of all study measurements, standard multidrug anti-tuberculosis treatment was initiated.

In the first part of the study, children received a single dose of RMP orally at 10 mg/kg body weight. In the second part, 10 mg/kg RMP in combination with 35 mg/kg EMB was given as a single dose after an adequate wash-out time of 1 week. Tablets were administered on an empty stomach after overnight fasting. Venipuncture was performed at 1, 2, 3, 4, 5, 7 and 24 h after medication. Samples were centrifuged within 30 min and the serum stored at −18°C.

RMP serum levels were measured by a microbiological method based on the agar diffusion disc technique in a modification previously described.[17] This was the standard technique 30 years ago, at the time the study was performed. A staphylococcus strain highly sensitive to RMP was used as the indicator strain. As staphylococcus strains are less sensitive to the main metabolite of RMP, desacetyl-rifampicin, than *M. tuberculosis*, assays with *Staphylococcus aureus* slightly underestimate the total activity against *M. tuberculosis*.[18] As the *S. aureus* strain was EMB-resistant, combination treatment had no influence on measurements of RMP, and RMP levels could also be determined when both drugs were given in combination. For further analysis, children were separated into three age groups: 2–<6 years (n = 7), 6–<10 years (n = 11) and 10–14 years (n = 9).

The mean RMP serum levels of all children were calculated for each time point. The means of the maximum serum levels (C_{max}) as well as the time until these levels were reached (T_{max}) were determined. Group analysis was performed using Student's t-test. The area under the serum concentration-vs.-time curve from time 0 to 7 h ($AUC_{0–7h}$) was determined by the linear trapezoideal rule.

RESULTS

The mean RMP serum levels after oral application of 10 mg/kg are shown in Figure 1 and the mean serum levels after combined administration of RMP (10 mg/kg) plus EMB (35 mg/kg) are shown in Figure 2. Tables 1 and 2 show the C_{max} and standard deviations (SDs), T_{max}, mean half-life and the $AUC_{0–7h}$ of RMP after single and combined treatment, respectively.

The mean serum levels of the different age groups showed a high variability, with mean maximum serum levels of 6.5–7.1 μg/ml in monotherapy and 4.5–5.4 μg/ml in combination therapy. Mean maximum serum concentrations in children aged <6 years after single and after combined drug administration tended to be lower than those found in the older children, although these differences fail to reach statistical significance. Compared to monotherapy, the mean maximum serum levels in combined therapy were lower in all age groups. These differences in maximum serum levels were up to 2.0 μg/ml, but again fail to reach statistical significance, probably due to the small sample size and a high variability in individual serum concentrations (data not shown). The mean T_{max} was

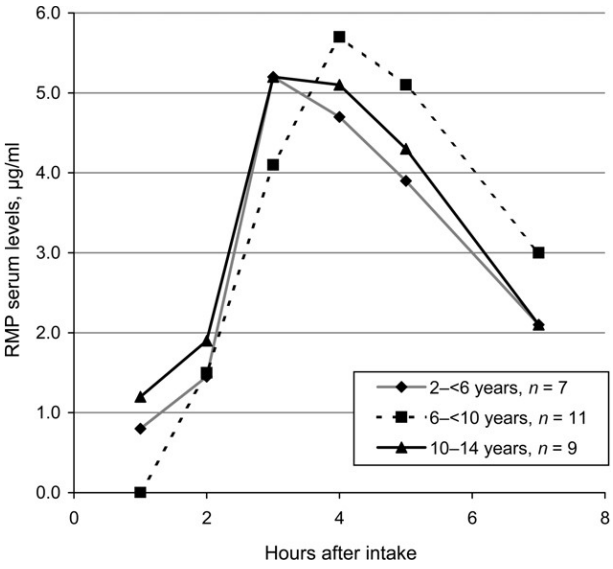

Figure 1 Mean serum levels of RMP among children in different age groups after the intake of RMP 10 mg/kg body weight in a single dose. RMP = rifampicin.

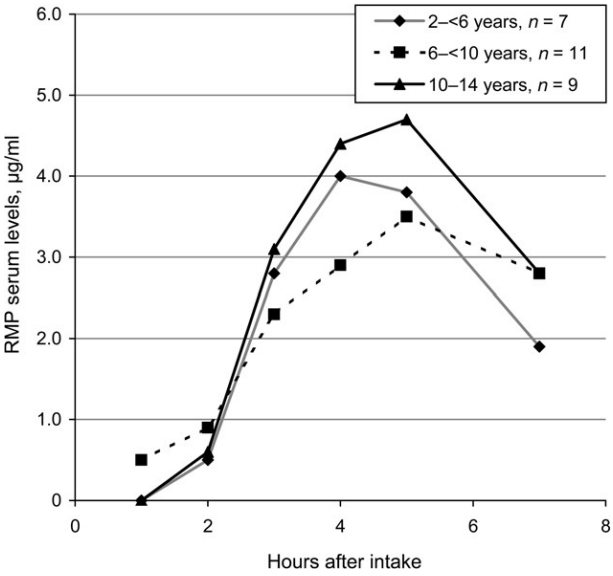

Figure 2 Mean serum levels of RMP among children in different age groups after combined administration of RMP 10 mg/kg + EMB 35 mg/kg body weight. RMP = rifampicin; EMB = ethambutol.

Table 1 Mean RMP serum levels and SDs among children in different age groups after intake of RMP 10 mg/kg in a single dose

	2–<6 years (n = 7) µg/ml (SD)	6–<10 years (n = 11) µg/ml (SD)	10–14 years (n = 9) µg/ml (SD)
Hours after ingestion			
1	0.8*	<0.4*	1.2*
2	1.5*	1.5*	1.9*
3	5.2 (1.9)	4.1 (1.3)	5.2 (0.2)
4	4.7 (0.9)	5.7 (1.1)	5.1 (0.6)
5	3.9 (0.6)	5.1 (0.9)	4.3 (0.7)
7	2.1 (0.3)	3.0 (0.4)	2.1 (0.2)
24	<0.4	<0.4	<0.4
C_{max}	6.5 (1.2)	7.1 (1.2)	6.6 (0.8)
T_{max}, h [min–max]	3.8 [3.0–5.0]	4.0 [4.0–5.0]	3.5 [1.5–5.0]
$t_{1/2}$, h	2.1	2.6	1.9
$AUC_{0–7h}$, µgh/ml	20.15	21.75	22.75

*As variability was high, SDs were not calculated.
RMP = rifampicin; SD = standard deviation; C_{max} = maximum serum level; T_{max} = time to maximum serum level; $t_{1/2}$ = elimination half-life; $AUC_{0–7h}$ = area under the serum concentration vs. time curve from time 0 to time 7 h.

3.5–4.3 h in all children, with only minor differences between the age groups and independently of whether monotherapy or combination therapy was received. Again, variability was high.

The elimination half-life was 1.9–2.6 h in monotherapy and 2.1–2.5 h in combination therapy. Children aged >10 years seemed to eliminate RMP faster than those aged <6 years. The $AUC_{0–7h}$ in all age groups on monotherapy was greater than that for combination therapy. In monotherapy, the $AUC_{0–7h}$ rose with age, while in combination therapy the age group 6–10 years had a lower $AUC_{0–7h}$ than the youngest children, whereas children aged >10 years had the highest $AUC_{0–7h}$.

Table 2 Mean RMP serum levels and SDs after ingestion of 10 mg/kg RMP in combination with 35 mg/kg EMB in children in different age groups

	2–<6 years (n = 7) µg/ml (SD)	6–<10 years (n = 11) µg/ml (SD)	10–14 years (n = 9) µg/ml (SD)
Hours after ingestion			
1	<0.4*	0.5*	<0.4*
2	0.5*	0.9*	0.6*
3	2.8 (1.0)	2.3 (0.7)	3.1 (0.6)
4	4.0 (1.1)	2.9 (0.6)	4.4 (0.8)
5	3.8 (0.9)	3.5 (0.7)	4.7 (0.7)
7	1.9 (0.3)	2.8 (0.8)	2.8 (0.4)
24	<0.4	<0.4	<0.4
C_{max}	4.5 (1.1)	5.3 (0.7)	5.4 (0.6)
T_{max}, h [min–max]	4.0 [3.5–5.0]	3.7 [2.0–5.0]	4.3 [3.0–5.0]
$t_{1/2}$, h	2.5	2.2	2.1
$AUC_{0–7h}$, µgh/ml	14.90	13.60	17.95

* As variability was high, SDs were not calculated.
RMP = rifampicin; SD = standard deviation; EMB = ethambutol; C_{max} = maximum serum level; T_{max} = time to maximum serum level; $t_{1/2}$ = elimination half-life; $AUC_{0–7h}$ = area under the serum concentration vs. time curve from time 0 to time 7 h.

DISCUSSION

In this study, RMP serum levels after oral intake of RMP alone and in combination with EMB in children of different age groups are described.

In children aged between 2 and 14 years, after a dosage of 10 mg/kg RMP is given, RMP serum levels are lower than those observed in adults after a standard dose of 600 mg. RMP serum levels in children are even lower if RMP is given in combination with EMB. RMP serum levels in adults after a standard oral dose of 600 mg RMP are in the range of 8–24 µg/ml 2 h postdose.[19,20] Serum levels in children in single or in combination therapy found in our study are even below the lower limit.

As low drug concentrations reduce therapeutic efficacy, higher doses of RMP than those currently recommended by the WHO (8–12 mg/kg) might therefore be necessary.[11]

Lower RMP serum levels after oral administration in children have been reported previously.[4,5,21,22] Serum levels in children treated with 10 mg/kg bodyweight were found to correspond to one third to one tenth of that in adults receiving 600 mg, and thus were similar to those in adults treated with a dose of 250 mg RMP.[4] On the other hand, serum levels of 9–11 µg/ml were found in another study in children where 10 mg/kg RMP was used as prophylaxis against *Haemophilus influenzae* type b disease.[23] This might be partly explained by the use of RMP suspension in this study, which could lead to improved RMP absorption. As a special in-house preparation for the RMP suspension was used, its pharmaceutical formulation might also differ from commercially available products, with possible impact on its pharmacokinetics and pharmacodynamics.

To our knowledge, no other studies have compared RMP serum levels in children after monotherapy with combination therapy with EMB. Similar to our findings in children, a decreased RMP area under the curve (AUC) has been reported in adults when the drug is given in combination with EMB.[22] Findings of serum levels of RMP given in combination therapy with INH are conflicting: both higher and lower RMP levels, as well as no change, have been described.[22–26] However, in combination therapy with INH and pyrazinamide (PZA), serum concentrations of RMP do not seem to differ from those with monotherapy.[24,26,27]

In the study, only a two-drug combination of RMP+EMB was examined to exclude the influence from other drugs, although in anti-tuberculosis treatment RMP is rarely given in combination with EMB alone. As the differences in RMP serum levels in mono- and combination therapy with EMB are not statistically significant, no conclusion can be drawn about

the clinical relevance of the lower RMP serum levels in combination therapy found in our study.

After oral intake of RMP, absorption from the intestinal tract is almost complete in adults, and peak serum levels are found after 2 h.[4,19,28] In children, absorption seems to be delayed, and peak serum levels were found after 4 h in our study, in line with previously reported findings.[4]

Unlike RMP absorption, there seems to be no major difference in elimination half-life ($t_{½}$) between adults and children. In adults, the $t_{½}$ is dose-dependent, and ranges from 2.3 h to 5.1 h, which is in line with our results and previously described findings of an average $t_{½}$ of 2.9 h in children after a 10 mg/kg dose of RMP.[7,23]

To explain these lower serum levels in children, different pharmacokinetic aspects have to be considered. Food has been shown to significantly reduce the absorption of RMP.[29] However, the children in our study received medication after overnight fasting.

Many more factors, such as gastric pH, gastric emptying, intestinal transit time, functional absorptive area, metabolic capacity and carrier mechanisms or drug transporters in the gastrointestinal tract, influence gastro-intestinal absorption of a drug.[19,30] However, as gastric pH, gastric emptying and intestinal transit time reach adult values within the first year of life, they would have a marginal influence on serum levels in older children compared to adults.[31] A decrease in the functional absorptive area of the intestine in TB patients has also been considered to explain reduced serum levels.[19] A prehepatic metabolism of RMP was described previously, probably localised in the gut wall in adults.[32] However, very little is known about the metabolic capacity or maturation of drug transporters in the gut wall in children and their influence on the quantity and time of absorption.[30]

Not only has delayed absorption been described in children but also a bioavailability of only 50% after oral administration of RMP.[33] RMP is well distributed throughout the body. As about 25% of the drug is ionised at a physiological pH, while the molecule as a whole is lipid-soluble, RMP concentrations in the various tissues of the human body differ.[6,7]

Observed differences in peak serum levels have mainly been attributed to age-related differences in extracellular body water compartments, which decrease from 45–60% in newborns to approximately 20% in adulthood.[4,7,22,31]

Although RMP is a strong inducer of the cytochrome P450 system, RMP itself is mainly metabolised in the liver by B-esterases.[34,35] Most liver enzymes mature after the first year of life.[31] As the half-life for serum levels and the appearance of RMP in the urine are similar in children and adults, maturation of these two systems probably has only a minor influence on RMP serum levels.[4–6]

The low maximum serum concentrations found in this study raise further questions regarding the clinical efficacy of RMP at a dosage of 10 mg/kg in childhood TB. In an in vitro study, it was shown that the efficacy of RMP is dependent on concentration rather than time.[36] This was also shown to be valid in vivo by a concentration-dependent drop in colony-forming units of *M. tuberculosis* in the sputum of patients with pulmonary TB as well as in clinical trials with different doses of RMP.[3,37,38] The EBA of a 1200 mg RMP dose was almost double that found at a dose of 600 mg RMP in adults.[39] Clinical outcome, as manifested by a lower rate of sputum conversion and a higher rate of treatment failures, was less good in patients with TB treated with dosages of 450 mg RMP per day than in patients treated with 600 mg per day.[38] RMP serum levels of 6–7 μg/ml, as found among children in our study, correspond to expected serum levels in adults after a dose of only 300–450 mg.[4]

Comparison of study results might be difficult because of the different analytical methods used. In the present study, a microbiological agar diffusion technique was used for the determination of RMP concentration, which was found to yield results that are essentially identical to those of high-performance liquid chromatography used today.[22] The staphylococcal strains used in the microbiological assay in this study are less sensitive to the main active metabolite of RMP, desacetyl-rifampicin, than *M. tuberculosis*. In adults, the metabolite concentrations are about 10% of those of the parent drug, and the total activity against *M. tuberculosis* might therefore be slightly underestimated in our study.[18] The amount of desacetyl-rifampicin of the parent drug in children is not known.

In children as well as in adults, there is considerable intra- and inter-individual variation in RMP serum levels, limiting the significance of data obtained from small study groups.[4,5,15] Taken together, a uniform dosage of 10 mg/kg RMP does not appear to be appropriate in children of all age groups, and especially not in children aged <6 years. In adults, RMP serum levels in continuous treatment are lower than at the beginning of treatment due to self-induction of RMP metabolisation.[4] As serum levels in this study in children were measured at the beginning of treatment, it implies that they would be even lower in continuous treatment. It is possible that even a single dose of RMP induces its own metabolisation; this could explain in part the lower RMP concentrations in combination therapy, where RMP is given for the second time.

As many physiological functions, including the water compartments at various ages, are proportional to body surface area (BSA), dosing according to body surface might be more appropriate.[40] An RMP dosage of 300 mg/m^2 BSA given to children at the age of 3 months to 2.9 years leads to mean RMP serum levels of 9.1 μg/ml, which is close to the desired serum level of 10 μg/ml.[29] We therefore assumed that efficient

serum levels should be achieved with an RMP dosage in children corresponding to the adult value of 350 mg/m^2 BSA (standard BSA in adults of 1.73 m^2 and a standard RMP dose of 600 mg), although these suggestions need to be validated by further studies. These calculations lead to a dosage of 15 mg/kg RMP in toddlers and young children, decreasing to 10 mg/kg RMP in adolescents.[41] ATS dosage recommendations of up to 20 mg/kg are even higher.[13]

Higher dosages always raise concerns about side effects. The most common side effects of RMP include gastrointestinal intolerance, elevation of liver enzymes and, in intermittent regimens, which are rarely applied to children, a flu-like syndrome.[35,42] RMP also turns urine, stool, sweat and plasma red. In adults, side effects are observed more frequently in doses above 900 mg.[27]

Reports of side effects of RMP in children are scarce. After an intravenous dosage of RMP of 20 mg/kg given to children, adverse effects (mainly cutaneous reactions) were observed frequently (five of nine patients).[42] In standard oral anti-tuberculosis regimens in children, RMP seems to be well tolerated.[37] After the single dose of RMP and EMB, none of the children in our study showed any side effect. In 567 children treated in our department between 1970 and 1980 for TB with a three- or four-drug regimen consisting of RMP, INH, EMB and PZA, the efficacy and toxicity of anti-tuberculosis treatment was evaluated retrospectively.[41] Only minor hepatotoxic side effects corresponding to RMP were found in 1.8% of the children.[41]

CONCLUSION

According to our study, the currently recommended RMP doses in childhood TB result in lower serum levels than in adults, running the risk of lower clinical efficacy.[11–13,20] Doses based on body surface (350 mg/m^2) might be more adequate for children. Larger studies are needed to validate these data and to base RMP doses in children on well-founded evidence.

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RÉSUMÉ

CONTEXTE : La rifampicine (RMP) est un médicament essentiel dans le traitement antituberculeux chez les enfants. Selon les recommandations actuelles de l'Organisation mondiale de la Santé, le dosage oral est de 10 (8–12) mg par kg de poids corporel.

OBJECTIF : Investiguer les niveaux sériques de RMP chez les enfants après administration orale de RMP seule ou après traitement en combinaison avec l'éthambutol (EMB).

SCHÉMA : Les niveaux sériques de RMP chez les enfants de différents groupes d'âge ont été déterminés après une administration unique de 10 mg/kg de RMP seule ainsi qu'après sa combinaison avec 35 mg/kg d'EMB.

RÉSULTATS : Les niveaux sériques de RMP sont plus faibles que ceux attendus chez les adultes recevant une dose orale similaire. Les niveaux sériques de RMP dans les traitements en combinaison sont même plus faibles qu'en cas de monothérapie.

CONCLUSION : Les dosages de RMP actuellement recommandés pour la tuberculose de l'enfant entraînent des taux sériques plus faibles que ceux recommandés chez les adultes, probablement en raison de différences pharmacocinétiques et pharmacodynamiques chez l'enfant. Chez les enfants, il semble plus valable de calculer la dose de la RMP sur base de la surface corporelle plutôt que sur base du poids corporel, ce qui entraînerait des doses plus élevées, particulièrement chez les jeunes enfants.

RESUMEN

MARCO DE REFERENCIA : La rifampicina (RMP) es un medicamento esencial en el tratamiento de la tuberculosis (TB) en los niños. Según las recomendaciones vigentes de la Organización Mundial de la Salud, la dosis oral es de 10 mg (8–12 mg) por kilogramo de peso corporal.

OBJETIVO : Analizar las concentraciones séricas alcanzadas con la administración oral de RMP sola o asociada con etambutol (EMB) en una población infantil.

MÉTODOS : Se determinaron las concentraciones séricas de RMP en niños de diferentes grupos de edad, después de la administración de una dosis única de10 mg/kg de RMP y de una asociación con 35 mg/kg de EMB.

RESULTADOS : Las concentraciones séricas de RMP fueron inferiores a las previstas en adultos que reciben una dosis oral equivalente. Con la administración combinada, las concentraciones de RMP fueron aún más bajas que con la monoterapia.

CONCLUSIÓN : Las dosis recomendadas actualmente para los niños en el tratamiento de la TB originan concentraciones séricas inferiores a las recomendadas en los adultos, probablemente en razón de las diferencias de la farmacocinética y la farmacodinamia. Pareciera que en los niños, el cálculo de la dosis de RMP en función de la superficie corporal fuese más adecuado que con respecto al peso ; esto implica pautas posológicas más altas, sobre todo en los niños más pequeños.

Adäquate RMP-Serumspiegel sind für den Therapieerfolg essentiell, insbesondere bei gravierenden TB-Manifestationen. Die TBM ist eine der schwersten Erkrankungsformen der TB im Kindesalter. Zwar stehen in Niedriginzidenzländern meist alle gängigen immunologischen und mikrobiologischen diagnostischen Tests zur Verfügung, zu deren Wertigkeit in der klinischen Routine bei TBM liegen bislang nur wenige Daten aus Niedriginzidenzländern vor.

3.4 Die Anwendung von immunologischen und mikrobiologischen Tests bei Kindern mit tuberkulöser Meningitis in Europa - eine multizentrische Studie der Paediatric Tuberculosis Netwerk European Trials Group (ptbnet)

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**geteilte Erstautorenschaft*

Im Rahmen des europäischen Netzwerkes „ptbnet“ haben wir die Anwendung immunologischer und mikrobiologischer Diagnostikverfahren bei Kindern mit TBM in Niedriginzidenzländern untersucht. Siebenundzwanzig europäische Zentren nahmen an dieser multizentrischen, retrospektiven Studie teil. Daten von 118 Kindern konnten gesammelt werden, von denen 54 (45,8%) eine gesicherte, 38 (32,2%) eine wahrscheinliche und 26 (22,0%) eine mögliche TBM hatten. Neununddreißig (33,1%) Kinder präsentierten sich initial mit einer milden Ausprägung (Grad I), 68 (57,6%) mit Grad 2 und 11 Kinder (9,3%) mit einer sehr schweren Ausprägung mit Bewusstseinstrübungen (Grad 3). Ein Großteil der Kinder erhielt eine cerebrale Bildgebung, bei der 83,3% mindestens eine zur Diagnose einer TBM passende Auffälligkeit zeigten. Der THT zeigte bei einem 5mm-cut-off-Wert eine Sensitivität von 61,9% und nur 50% bei einem cut-off von 10mm. Die Sensitivität des QuantiFERON-TB® und T-SPOT.TB® Tests lagen bei 71,7% und 82,5%, wobei „indeterminate“ Ergebnisse mit 17%

der Fälle häufig waren. *M. tuberculosis* konnte bei 50% der Kinder in der Kultur aus Liquor nachgewiesen werden, der Nachweis mittels PCR gelang in 34,8% der Fälle. Bei den Kindern, bei denen der THT, IGRA, Liquorkultur und Liquor-PCR durchgeführt wurden, lag die diagnostische Sensitivität bei Positivität mindestens eines Testverfahrens bei 84,4%. Zusätzlich hinweisend auf eine TB können im Röntgen-Thorax erfasste Veränderungen sein, die bei fast drei Viertel der Kinder in unserer Kohorte vorlagen. Trotz Verfügbarkeit der aktuellen diagnostischen Möglichkeiten, wird bei 1 von 5 Kindern möglicherweise die Diagnose einer TBM nicht gestellt werden. Es bedarf daher dringend einfach anzuwendender, optimalerweise direkt verfügbarer (im Sinne eines point-of-care Tests) Diagnostika, um alle Kinder mit TBM zu erfassen und eine entsprechende Therapie einzuleiten.

Performance of immune-based and microbiological tests in children with tuberculosis meningitis in Europe: a multicentre Paediatric Tuberculosis Network European Trials Group (ptbnet) study

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All existing immunological and microbiological TB tests have suboptimal sensitivity in children with TBM. Combining immune-based tests with CSF culture and PCR results in far higher positive diagnostic yields, and should therefore be standard practice. http://bit.ly/2TSAArl

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ABSTRACT

Introduction: Tuberculous meningitis (TBM) is often diagnostically challenging. Only limited data exist on the performance of interferon-γ release assays (IGRA) and molecular assays in children with TBM in routine clinical practice, particularly in the European setting.

Methods: Multicentre, retrospective study involving 27 healthcare institutions providing care for children with tuberculosis (TB) in nine European countries.

Results: Of 118 children included, 54 (45.8%) had definite, 38 (32.2%) probable and 26 (22.0%) possible TBM; 39 (33.1%) had TBM grade 1, 68 (57.6%) grade 2 and 11 (9.3%) grade 3. Of 108 patients who underwent cranial imaging 90 (83.3%) had at least one abnormal finding consistent with TBM. At the 5-mm cut-off the tuberculin skin test had a sensitivity of 61.9% (95% CI 51.2–71.6%) and at the 10-mm cut-off 50.0% (95% CI 40.0–60.0%). The test sensitivities of QuantiFERON-TB and T-SPOT.TB assays were 71.7% (95% CI 58.4–82.1%) and 82.5% (95% CI 58.2–94.6%), respectively (p=0.53). Indeterminate results were common, occurring in 17.0% of QuantiFERON-TB assays performed. Cerebrospinal fluid (CSF) cultures were positive in 50.0% (95% CI 40.1–59.9%) of cases, and CSF PCR in 34.8% (95% CI 22.9–43.7%). In the subgroup of children who underwent tuberculin skin test, IGRA, CSF culture and CSF PCR simultaneously, 84.4% had at least one positive test result (95% CI 67.8%–93.6%).

Conclusions: Existing immunological and microbiological TB tests have suboptimal sensitivity in children with TBM, with each test producing false-negative results in a substantial proportion of patients. Combining immune-based tests with CSF culture and CSF PCR results in considerably higher positive diagnostic yields, and should therefore be standard clinical practice in high-resource settings.

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Introduction

Globally, an estimated 1 million children and adolescents develop active tuberculosis (TB) annually, with the majority of the disease burden occurring in low-resource countries [1]. In most European countries the incidence of TB disease has been declining steadily over recent decades, but drug-resistant *Mycobacterium tuberculosis* has brought new challenges, particularly in Eastern Europe [2].

TB meningitis (TBM) is an uncommon manifestation of TB disease, but is associated with significant morbidity and mortality, even in high-resource settings [3]. Children with TBM frequently present with nonspecific symptoms and without a history of TB contact, and diagnosing TBM is therefore often challenging [4–6]. Importantly, previous data suggest that delays in diagnosis are linked to poor outcomes [7].

TB diagnostics used in routine clinical practice have evolved significantly over the past two decades, with the introduction of interferon-γ release assays (IGRAs) and a variety of commercial molecular assays [8]. Recent data show that both IGRAs and molecular TB assays are widely available across Europe, and are used extensively by paediatric TB specialists [9, 10].

Immune-based TB tests, comprising tuberculin skin tests (TSTs) and IGRAs, are commonly used as adjunctive diagnostic tools in children with suspected TB disease [8], but the existing data on the performance of IGRAs specifically in children with TBM remain very limited [11, 12]. In addition, although a small number of studies have investigated the use of molecular TB assays in children with suspected TBM, most of these were small, limited to a single study site, or from low-resource settings where late presentations are likely to be more common than in Europe [4, 13, 14]. Furthermore, most studies were conducted under protocolised study conditions, and therefore prone to overestimating test sensitivity compared to performance in routine clinical settings.

This study aimed to determine the sensitivity of immunological, conventional microbiological and molecular TB tests in children with TBM in the context of routine clinical care in Europe. Secondary aims were to describe clinical features and radiological findings at presentation, and to evaluate the Uniform TBM Research Case Definition (UTRCD) score in the European setting.

Methods

European members of the Paediatric Tuberculosis Network European Trials Group (ptbnet), which at that point in time included 214 clinicians and researchers based in 31 European countries [9, 10, 15, 16], were invited to retrospectively report children and adolescents (aged 0–16 years) with TBM who had received healthcare at their institution. The study opened in February 2016 and reporting closed in August 2016. Data were collected via a web-based tool creating a standardised dataset for each case. The study was reviewed and approved by the human ethics committee of the Charité Universitätsmedizin Berlin and the ptbnet steering committee. No personal or identifiable data were collected during the conduct of this study.

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Classification of cases

Cases were categorised as definite TBM, probable TBM or possible TBM, according to consensus definitions based on the UTRCD score (supplementary table S1) [3], with minor modifications, as follows. The item "history of close contact with an individual with pulmonary TB or a positive TST or IGRA", scoring 2 points in the original criteria was split into two separate items: 1) history of close contact with an individual with pulmonary TB and 2) a positive TST (⩾10 mm) and/or IGRA, each scoring one point if present. Furthermore, "choroidal tubercles" was added to the category "evidence of tuberculosis elsewhere", scoring 1 point if present; the maximum category score of 4 was retained. If no data were available for one particular item, the respective item was scored as 0. Briefly, definite TBM was defined as a patient with clinical entry criteria (headache, irritability, vomiting, fever, neck stiffness, convulsions, focal neurological deficits, altered consciousness or lethargy) plus one or more of the following: acid-fast bacilli detected in cerebrospinal fluid (CSF), *M. tuberculosis* cultured from CSF or *M. tuberculosis* detected by PCR in CSF. Probable TBM was defined as presence of clinical entry criteria plus a total diagnostic score of ⩾12, and possible TBM as presence of clinical entry criteria plus a total diagnostic score of 6–11.

Disease severity

Disease severity was graded according to the modified British Medical Research Council (BMRC) criteria [17, 18]. In brief, grade 1 corresponds to a Glasgow coma score of 15 with no neurological signs, grade 2 a score of 11–14 or a score of 15 with focal neurological signs, and grade 3 a score of ⩽10.

Statistical analysis

Nonparametric two-tailed Mann–Whitney U-tests were used to compare continuous variables. The sensitivities of diagnostic tests were compared using two-tailed Fisher's exact tests. In cases where a TST was performed and reported as negative, but with no result of induration in millimetres available, it was considered as missing data at the 5-mm threshold and as a negative result at the 10-mm threshold; if a TST was reported as positive without induration size, it was considered as positive at the 10-mm threshold, and hence also positive at the 5-mm threshold. The 95% confidence intervals around proportions were calculated using the Wald method. Multivariate logistic regression analyses were carried out for associations between positive IGRA, positive TST (at the 5-mm and 10-mm thresholds) and indeterminate IGRA as outcome variables, with predictor variables of age, sex, bacille Calmette–Guérin (BCG) vaccination status, TBM staging and definite TBM diagnosis. Models were evaluated using the Hosmer–Lemeshow goodness-of-fit test and receiver operating characteristic curves showed an area under the curve ⩾0.7. The primary outcome measures were odds ratios. The 95% confidence interval was calculated for each odds ratio, and p-values <0.05 were considered significant. Analyses were done using Prism (version 8.0; GraphPad, La Jolla, CA, USA) and Stata (version 12.1; StataCorp, College Station, TX, USA). The study is reported in accordance with Standards for Reporting of Diagnostic Accuracy Studies guidelines.

Results

27 healthcare institutions, situated in Bulgaria (n=1), Finland (n=1), Germany (n=3), Greece (n=1), Italy (n=3), Slovenia (n=1), Spain (n=12), Sweden (n=2) and the United Kingdom (n=3), contributed cases to the study.

118 children were included in the final analysis, comprising 54 (45.8%) definite, 38 (32.2%) probable and 26 (22.0%) possible TBM cases. With regards to disease severity, 39 (33.1%) were BMRC TBM grade 1, 68 (57.6%) grade 2 and 11 (9.3%) grade 3.

The demographic details are shown in table 1. The median (interquartile range (IQR)) age was 2.7 (1.1–6.4) years. Although the majority (89.8%) of children had been born in Europe, almost half of these (48.3%) were from families with one or both parent(s) originating from a country with high TB prevalence. Almost half (41.5%) had a history of TB contact. A test for HIV was performed in 73 (61.9%) children; only two (2.7%) were positive.

The commonest constitutional symptom at presentation was fever. The most common neurological symptoms at presentation comprised vomiting, headache and altered level of consciousness (table 1).

Distribution of the UTRCD score among subgroups

In the group of patients with definite TBM the mean±SD score was 12.8±3.1 (range 4–19). In the patients with probable or possible TBM combined, the mean score was 12.1±2.8 (6–18). Of the children with definite TBM, almost one-third (n=17, 31.5%) had scores <12 (figure 1).

Radiological investigations

Of 112 patients who underwent chest radiography, 81 (72.3%) had changes suggestive of intrathoracic TB disease, including hilar lymphadenopathy, pulmonary infiltrates, consolidation or cavitation (table 2). In 26 (22.8%) cases miliary infiltrates were identified.

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TABLE 1 Baseline demographic data and clinical features at presentation

Age years	2.7 (1.1–6.4)
Male:female	1.1:1.0
Born in Europe	106 (89.8)
Born in Europe with one or both parent(s) originating from a high TB incidence country	57 (48.3)
Born outside Europe	12 (10.2)
Africa	6 (50.0)
Asia	3 (25.0)
South America	3 (25.0)
Prior BCG vaccination	
Yes	22 (18.6)
No	80 (67.8)
Unknown	16 (13.6)
Known TB contact	
Yes	49 (41.5)
No	67 (56.7)
Unknown	2 (1.7)
Constitutional symptoms at presentation	
Fever	99 (83.9)
Weight loss	32 (27.1)
Night sweats	10 (8.5)
Neurological symptoms at presentation	
Vomiting	70 (59.3)
Altered consciousness	55 (46.6)
Headache	52 (44.1)
Lethargy	27 (22.9)
Cranial nerve palsy	26 (22.0)
Seizures	25 (21.2)
Ataxia	5 (4.2)
Paresis	3 (2.5)

Data are presented as median (interquartile range), n or n (%). TB: tuberculosis; BCG: bacille Calmette–Guérin.

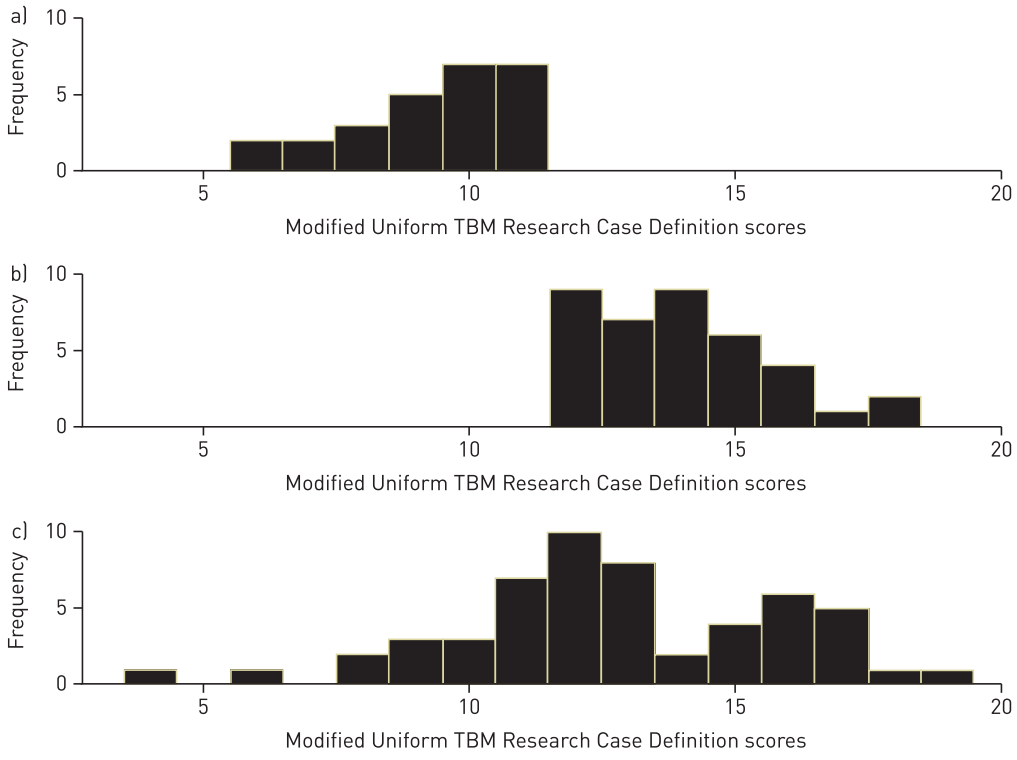

FIGURE 1 Distribution of modified Uniform Tuberculous Meningitis Research (TBM) Case Definition scores among cases with a) possible, b) probable and c) definite tuberculous meningitis.

TABLE 2 Radiological findings on chest radiography, abdominal ultrasound scan and cranial imaging with computed tomography (CT) or magnetic resonance imaging (MRI)

Chest radiography	112
Changes suggestive of active TB[#]	81 (72.3)
Changes suggestive of previous pulmonary TB[¶]	2 (1.8)
No abnormalities detected	29 (25.9)
Abdominal ultrasound scan	65
Hepatomegaly	10 (15.4)
Splenomegaly	9 (13.8)
Intra-abdominal granulomas	11 (16.9)
Miliary lesions	4 (6.2)
Enlarged lymph nodes	2 (3.1)
No abnormalities detected	42 (64.6)
Cranial CT/MRI	108
Hydrocephalus	53 (49.1)
Basal meningeal enhancement	44 (40.7)
Intracranial tuberculomas	32 (29.6)
Cerebral infarcts	14 (13.0)
No abnormalities detected	18 (16.7)

Data are presented as n or n (%). TB: tuberculosis. [#]: hilar adenopathy, pulmonary infiltrates, consolidation or cavitation; [¶]: fibrotic scars or calcification.

65 patients had an abdominal ultrasound scan. In the majority (64.6%), no abnormalities were detected. The most common abnormal findings were hepatomegaly, splenomegaly and intrabdominal granulomas (table 2).

In 108 patients, cranial imaging with computed tomography and/or magnetic resonance imaging was performed. Of those, 90 (83.3%) had one or more abnormal findings consistent with TBM. The most common finding was hydrocephalus, followed by basal meningeal enhancement and intracranial tuberculomas (table 2). In the remaining 18 (16.7%) patients, no significant abnormalities were identified, which included six children with definite TBM.

Performance of immunological TB tests

TST, QuantiFERON Gold assay and T-SPOT.TB assay (both performed on blood samples) results were available in 92, 53 and 17 patients, respectively. In 10 patients neither TST nor IGRA results were available.

Table 3 summarises the results of 108 patients in whom TST and/or IGRA results were available. Of the 54 children in whom both TST and IGRA results were available only six (11.1%) had concordantly negative TST (at the 10-mm threshold) and IGRA results; five (9.3%) had negative TST and indeterminate QFT results; in the remaining 43 (79.6%), at least one immunological test result was positive.

At the 5-mm cut-off the TST had a sensitivity of 61.9% (95% CI 51.2–71.6%), and at the 10-mm cut-off 50.0% (95% CI 40.0–60.0%). The sensitivities of the QFT and the T-SPOT.TB assay were 71.7% (95% CI

TABLE 3 Summary of tuberculin skin test (TST) and interferon-γ release assay (IGRA) results in patients who had at least one immunological test performed

	Patients	QFT positive	QFT negative	QFT indeterminate	T-SPOT positive	T-SPOT negative	T-SPOT indeterminate	No IGRA[#]
TST cut-off 5 mm[¶]	84							
Positive		18 (21.4)	1 (1.2)	1 (1.2)	8 (9.5)	0	0	24 (28.5)
Negative		9 (10.7)	2 (2.4)	3 (3.6)	4 (4.8)	2 (2.2)	0	12 (14.3)
TST cut-off 10 mm	92							
Positive		16 (17.4)	1 (1.1)	1 (1.1)	6 (6.5)	0	0	22 (23.9)
Negative		13 (14.1)	4 (4.3)	5 (5.4)	6 (6.5)	2 (2.2)	0	16 (17.4)
No TST[+]	16	9 (56.3)	1 (6.3)	3 (18.8)	2 (12.5)	1 (6.3)	0	

Data are presented as n or n (%). n=108. QFT: QuantiFERON-TB Gold assay; T-SPOT: T-SPOT.TB assay. [#]: IGRA not performed or result not available; [¶]: excludes eight patients who were negative at the 10-mm cut-off, but had no quantitative result recorded; [+]: TST not performed or result not available.

58.4–82.1%) and 82.5% (95% CI 58.2–94.6%), respectively. Statistically, there was no significant difference between the sensitivity of the TST at the 5-mm cut-off and the QFT assay (0.27); however, there was a significant difference at the 10-mm cut-off (p=0.0143). Similarly, no significant difference was detected between the TST at 5 mm and the T-SPOT.TB assay (p=0.16), but there was a significant difference at the 10 mm cut-off (p=0.0167). There was no statistically significant difference between the sensitivity of both IGRA assays (p=0.53). The proportion of positive TST results (at the 10-mm cut-off) did not differ significantly between BCG-vaccinated and BCG nonvaccinated children (47.1% *versus* 52.5%; p=0.78); in addition, there was no significant difference between those two subgroups with regards to TST induration size (median 8 mm *versus* 10 mm; p=0.81).

Of the 53 patients with QFT results, nine (17.0%) had an indeterminate test result (95% CI 9.0–29.5%). In the 17 patients with T-SPOT.TB results, there were no indeterminate results. There was no statistical difference between both IGRAs with regards to the proportion of indeterminate *versus* determinate (*i.e.* positive or negative) results (p=0.10). On average children with indeterminate test results were younger (median (IQR) age 2.0 (1.4–3.0) years) than children with determinate results (2.7 (1.0–6.5) years), although this did not reach statistical significance (p=0.22) (supplementary table S2).

CSF results

The CSF results at initial presentation in the 106 patients in whom those data were available are summarised in figure 2 and supplementary table S3. Only 10 (9.4%) patients had CSF protein concentrations within the normal range (0–0.4 $g{\cdot}L^{-1}$); in 57 (53.8%) patients, the CSF protein concentration was $\geqslant$1.0 $g{\cdot}L^{-1}$.

Performance of microbiological tests with CSF

Results of acid-fast stains, mycobacterial culture and *M. tuberculosis* PCR testing on CSF were available in 75, 94 and 69 patients, respectively. Only three (4.0%) cases were positive for acid-fast bacilli (sensitivity 95% CI 0.9–11.6). 47 (50.0%) cases had positive mycobacterial culture results (95% CI 40.1–59.9%), while only 24 (34.8%) were positive on PCR testing (95% CI 22.9–43.7%), although this did not reach statistical significance (p=0.06). Of the 62 cases in whom both mycobacterial culture and PCR had been performed on CSF, 17 were positive in both tests, 15 were positive only in culture, and four positive only in PCR. In this subgroup, performing both tests in parallel achieved greater sensitivity (36 (58.1%) out of 62, 95% CI

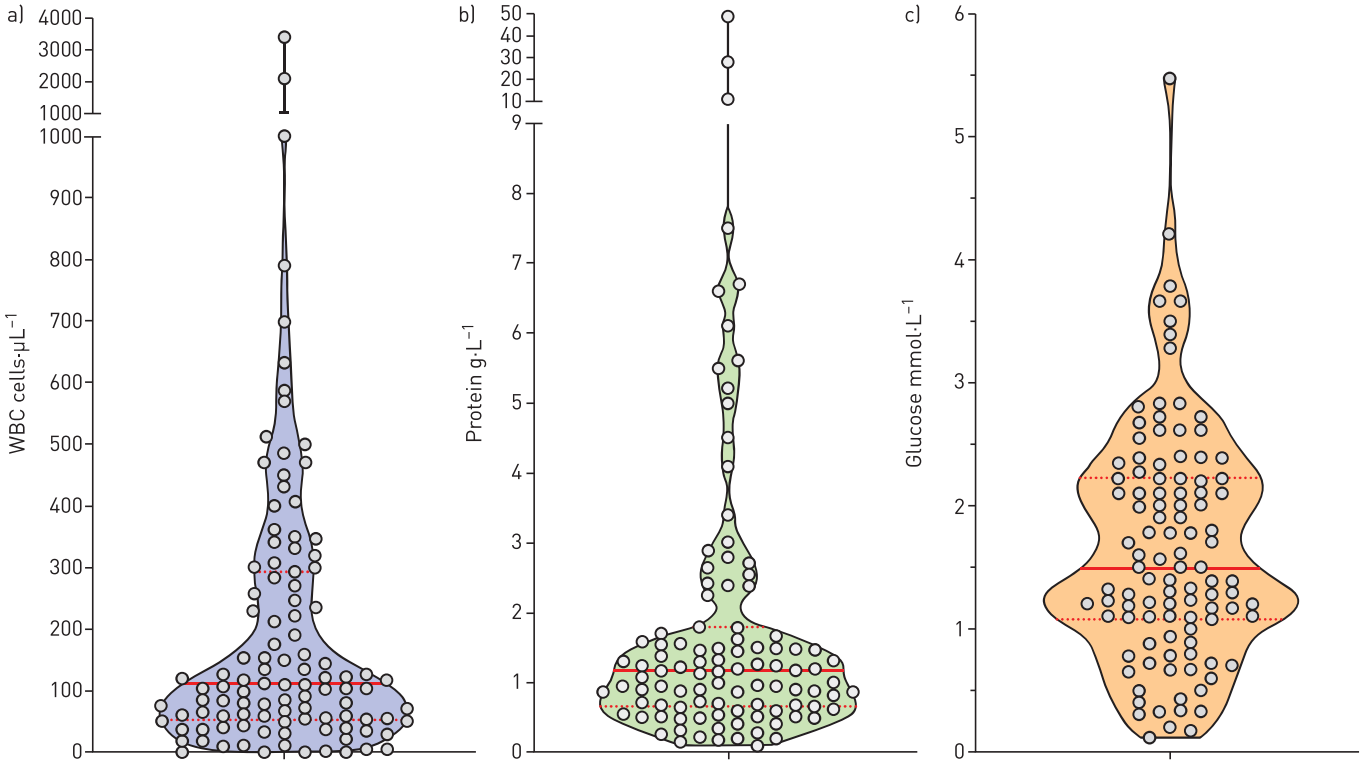

FIGURE 2 Violin plots of cerebrospinal fluid white blood cell counts (WBC), protein and glucose concentrations at initial presentation. Horizontal lines indicate the medians and interquartile ranges.

45.7–69.5%) than performing either culture (32 (51.6%) out of 62, 95% CI 39.5–63.6%) or PCR alone (21 (33.9%) out of 62, 95% CI 23.3–46.3%), but only the comparison with PCR alone was statistically significant (p=0.59 and p=0.0113, respectively).

Combining immunological and microbiological tests

Figure 3 summarises the results of the subgroup of patients in whom both immunological and both mycobacterial culture and PCR on CSF had been performed (n=32), showing that TST-positive/IGRA-positive/CSF culture-positive and IGRA-positive only were the most common result constellations, but also that result constellations were very heterogeneous. Only five (15.6%) cases had negative results in all four tests; therefore, the overall sensitivity of all four tests combined was 84.4% (95% CI 67.8%–93.6%). Only one of those five cases had sampling performed at another site, a lymph node biopsy that was culture- and PCR-positive for *M. tuberculosis*.

Multivariate logistic regression analyses

The results of the multivariate regression analyses for having a positive immunological test result are summarised in table 4. Children with TBM grade 3 were significantly less likely to have a positive TST (at both the 5-mm (OR 0.08, p=0.019) and the 10-mm cut-off (OR 0.06, p=0.023)) than those with TBM grade 1. However, this was not a statistically significant predictor of a positive IGRA result (OR 0.13, p=0.13). Younger children were more likely to have a positive IGRA result (OR 0.7 per year of increasing age, p=0.042). There were no statistically significant predictor variables of an indeterminate IGRA result in multivariate analysis (supplementary table S2).

Detection of M. tuberculosis *at other sites*

In 56 (47.5%) patients *M. tuberculosis* was detected in at least one clinical sample other than CSF (table 5). Of those, 49 (87.5%) were culture-positive and 27 (48.2%) were PCR-positive; 20 (35.7%) were positive in both culture and PCR. Among the 64 cases with possible and probable TBM (*i.e.* in whom *M. tuberculosis* was not identified in the CSF), *M. tuberculosis* was identified by culture and/or PCR at another site in 30 (46.9%) cases, securing a microbiological diagnosis in those patients.

Discussion

To our knowledge, this is the largest multicentre study on TBM in children from a low TB incidence setting to date, facilitated by inclusion of a large number of participating centres across Europe via a well-established collaborative paediatric TB research network.

That this study was conducted in a low TB incidence setting is relevant for the interpretation of its findings. Almost a third (33.1%) of the cases had BMRC TBM grade 1 disease, while only 9.3% had grade 3 disease, contrasting with reports from high TB incidence countries, where the vast majority of patients have grade 2 or grade 3 disease at presentation [13]. This indicates that in the European setting there is a tendency for patients with TBM to present earlier and with less severe disease.

In addition, our cohort differs from most cohorts of children with TBM reported from high TB prevalence countries with regards to the proportion of cases that are microbiologically confirmed. Almost half

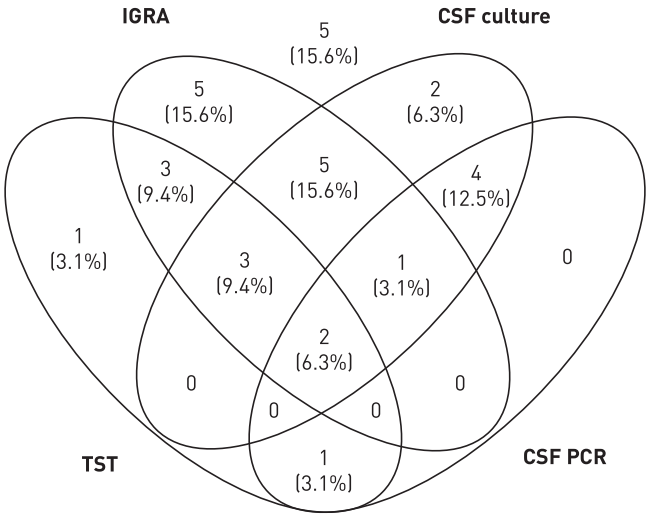

FIGURE 3 Venn diagram summarising positive tuberculin skin test (TST), interferon-γ release assay (IGRA) and cerebrospinal fluid (CSF) test results (culture and PCR) in the subgroup of patients who had all four tests performed (n=32). In five of those patients (shown above the diagram), all four tests were negative.

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TABLE 4 Multivariate logistic regression analysis for association between positive tuberculin skin test (TST) at the 5-mm and the 10-mm threshold, and positive interferon-γ release assay result (IGRA$^+$) as outcome variable, and predictor variables of age, sex, bacille Calmette–Guérin (BCG) vaccination status, tuberculosis meningitis (TBM) staging, definite TBM diagnosis and IGRA type (for IGRA result only)

	Descriptor	Outcome variable (positive result)	OR (95% CI)	p-value
Age years	Continuous	TST 5 mm	0.89 (0.78–1.02)	0.100
		TST 10 mm	0.90 (0.79–1.02)	0.103
		IGRA$^+$	**0.70 (0.50–0.99)**	**0.042**
Male	Binary	TST 5 mm	0.43 (0.14–1.29)	0.133
		TST 10 mm	0.61 (0.22–1.66)	0.331
		IGRA$^+$	0.66 (0.16–2.69)	0.560
BCG status	Binary	TST 5 mm	1.60 (0.33–7.71)	0.560
		TST 10 mm	1.27 (0.29–5.50)	0.751
		IGRA$^+$	1.52 (0.13–18.08)	0.740
TBM staging	Categorical			
Stage 2 compared to stage 1		TST 5 mm	0.36 (0.11–1.21)	0.100
		TST 10 mm	0.43 (0.15–1.25)	0.121
		IGRA$^+$	0.25 (0.03–1.85)	0.180
Stage 3 compared to stage 1		TST 5 mm	**0.08 (0.01–0.65)**	**0.019**
		TST 10 mm	**0.06 (0.00–0.68)**	**0.023**
		IGRA$^+$	0.13 (0.01, 1.82)	0.129
Definite TBM diagnosis	Binary	TST 5 mm	0.71 (0.24–2.10)	0.540
		TST 10 mm	0.37 (0.13–1.03)	0.056
		IGRA$^+$	0.82 (0.19–3.64)	0.798
Type of IGRA assay	Binary			
T-SPOT.TB compared to QFT		IGRA$^+$	22.15 (0.79–623.49)	0.069

Indeterminate IGRA results were classified as negative for this analysis. Bold type represents p<0.05. T-SPOT: T-SPOT.TB assay; QFT: QuantiFERON-TB Gold assay.

(45.8%) of the cases in our cohort were confirmed, contrasting with studies from high prevalence settings in which fewer than a quarter were confirmed cases [14, 19, 20]. This may be the result of recall bias and preferential reporting of confirmed cases in our study, or alternatively may reflect the greater availability of diagnostic tests at the centres that participated in this study compared to lower resource settings. The latter hypothesis is supported by the fact that paediatric studies in high TB prevalence settings with access to molecular diagnostics have reported similar proportions of microbiologically confirmed cases [4, 21].

The performance of the UTRCD scoring system, which is based on expert consensus [3], was suboptimal in our cohort. Almost one-third (31.5%) of cases with microbiologically confirmed TBM had scores <12, which in the absence of a positive microbiological result would categorise those patients as "possible TBM". It is possible that the comparatively poor performance relates to the tendency for European patients to present earlier (and therefore with fewer features and consequently lower scores) than patients in high TB prevalence settings. However, in some patients, certain data required for scoring (*e.g.* symptom duration) were not recorded, potentially resulting in the UTRCD scores of those patients being skewed towards lower values. However, importantly, this scoring system was developed for research purposes, and not for clinical decision-making.

TABLE 5 Summary of microbiological test results of samples other than cerebrospinal fluid

	Patients	Positive for AFB	Positive in culture	Positive in PCR
Sputum	8	1 (12.5)	6 (75.0)	0
Gastric aspirates	42	10 (23.8)	37 (88.1)	18 (42.9)
Nasopharyngeal aspirate	5	1 (20.0)	4 (80)	3 (60.0)
Bronchoalveolar lavage fluid	7	3 (42.9)	6 (85.7)	3 (42.9)
Lymph node material	4	0	3 (75.0)	3 (75.0)

Data are presented as n or n (%). AFB: acid-fast bacilli.

Radiological changes suggestive of intrathoracic TB disease were present in almost three-quarters (72.3%) of the cases. This highlights that patients with suspected TBM should routinely undergo chest imaging, as this is likely to provide useful information aiding diagnosis. However, our data contrast with data from other studies that reported chest radiography changes in considerably lower proportions of children with TBM, typically 40–60% [19, 22, 23]. The observation that a high proportion (83.3%) of children in our cohort had abnormal findings on cranial imaging, including hydrocephalus, basal meningeal enhancement and intracranial tuberculomas, is consistent with previous reports [19, 20, 22].

Our data highlight that all existing immunological and microbiological TB tests have suboptimal sensitivity in children with TBM. TST, QFT assays and T-SPOT.TB assays had sensitivities of ∼80% or below, indicating that approximately one in five children with TBM have a false-negative result when a single immunological test is performed, irrespective of which test is used. Several recent studies, including in patients with TBM, have investigated novel immune-based TB biomarkers in blood that have the potential to improve the diagnosis of TB in children, but additional studies will be required to confirm their findings [24–26]. Interestingly, our multivariate logistic regression analyses indicate that false-negative TST results were more common in children with more severe TBM. Furthermore, we found that a large proportion of patients had discordant TST and IGRA results, in accordance with observations reported by studies in children with pulmonary TB [24, 27, 28].

It was striking that a substantial proportion of children had indeterminate IGRA test results. Among children who had undergone testing with QFT assays, 17.0% had an indeterminate result, which is considerably higher than in most studies that investigated the performance of QFT assays in children with pulmonary TB [24, 27, 29, 30]. Interestingly, the association between tuberculous central nervous system (CNS) disease and indeterminate IGRA results was also observed in a Californian study, which only included 17 confirmed cases with CNS disease [11]. Although the basis for these observations remains uncertain, it is tempting to hypothesise that age is a contributing factor, considering that the median age of our cohort was 2.6 years, but we did not detect an association between age and indeterminate test results in multivariate logistic regression analyses. Nevertheless, several published studies, including our own, have shown that young age is associated with indeterminate IGRA results [31–33]. Alternatively, there may be immunological differences between children with TBM and those with pulmonary TB, resulting in impaired IGRA performance in the former.

In accordance with published data our results show that acid-fast bacilli stain microscopy has very poor sensitivity in children with TBM [7, 14, 22]. Mycobacterial culture performed on CSF was the microbiological test with the highest sensitivity, but still only positive in half of the cases. PCR for *M. tuberculosis* performed on CSF had even lower sensitivity, producing a positive result in only approximately one in three cases. However, the fact that a variety of in-house and commercial PCR assays were used at different healthcare institutions limit the interpretation of this finding. A recent study that included 23 HIV-infected adults with TBM found that the recently released Xpert MTB/RIF Ultra assay had higher sensitivity than both the previous generation Xpert MTB/RIF assay and culture (sensitivity 70% *versus* 43% and 43%, respectively) [34], suggesting that some commercial PCR-based assays may perform as well as culture or potentially even have superior sensitivity in TBM. However, larger prospective studies are needed to confirm those findings. Our data show that performing both culture and PCR on CSF in parallel increases the diagnostic yield, in concordance with observations in a paediatric study from South Africa [21]. A recent publication raises hopes that metagenomic next-generation sequencing of CSF could potentially improve the diagnosis of CNS infections with organisms that are difficult to detect with existing microbiological methods [35].

In addition, our data show that in the large majority of children with TBM at least one test produces a positive result if TST, IGRA, CSF culture and CSF PCR are performed in parallel, as only 15.6% of the cases showed false-negative results in all four tests. In the paediatric setting immunological tests are often used as adjunctive tests in suspected TB disease [8], a practice that is supported by our findings. Although positive immunological tests do not confirm TB disease, in a child with compatible clinical and radiological findings they lend substantial support to a putative diagnosis of TBM.

In a substantial number of children in this cohort *M. tuberculosis* was detected in samples other than CSF, helping to secure a microbiological diagnosis. Sputum, gastric aspirates and bronchoalveolar lavage fluid samples all had high yields, universally with a positive detection rate of ⩾75%. However, considering that decisions to obtain those samples were made by clinicians managing the patients, rather than according to a standardised study protocol, it is probable that these samples were preferentially obtained in a selected group of patients who had chest radiography changes or respiratory symptoms. Nevertheless, our data highlight that testing respiratory/gastric samples should be undertaken routinely in children with suspected TBM, as *M. tuberculosis* can often not be detected in CSF, precluding microbiological confirmation and susceptibility testing.

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As with all retrospective studies, a key limitation is that some data were missing due to incomplete documentation. A larger number of patients had TSTs performed, but only categorical rather than quantitative data were documented, resulting in those patients having to be excluded from some of the analyses. Additionally, only a small number of participating centres were using T-SPOT.TB assays; consequently, the data on the performance of this test were limited. No cases had IGRAs performed on CSF; however, a recent meta-analysis has shown that performing IGRAs on CSF rather than blood does not result in a higher diagnostic yield [12]. Finally, in common with all retrospective studies, there is a risk of recall bias and preferential reporting.

In conclusion, our data show that in the European setting children with TBM tend to present earlier and with less severe disease than in high TB incidence settings. A large proportion of children with TBM have coexisting intrathoracic TB disease, and consequently chest imaging and collection of respiratory or gastric samples should be considered in all patients with suspected TBM. Both immunological (TST and IGRAs) and microbiological TB tests have suboptimal sensitivity in children with TBM. Performing both TST and IGRA in parallel with microbiological testing of CSF by culture and PCR results in a substantial increase in the proportion of children who have evidence of TB infection, which should therefore be the standard approach in healthcare settings with sufficient resources to perform those tests.

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Daten zur Versorgung von Kindern mit TBM aus Niedriginzidenzländern lagen bislang nur begrenzt vor. Wir untersuchten an derselben Kohorte wie in der vorangegangenen Arbeit die Therapie und das Outcome von Kindern mit TBM in Europa.

3.5 Therapie und Outcome bei Kindern mit tuberkulöser Meningitis – eine multizentrische Studie der Paediatric Tuberculosis Network European Trials Group

Thee S, Basu Roy R, Blázquez-Gamero D, Falcón-Neyra L, Neth O, Noguera-Julian A, Lillo C, Galli L, Venturini E, Buonsenso D, Götzinger F, Martinez-Alier N, Velizarova S, Brinkmann F, Welch SB, Tsolia M, Santiago-Garcia B, Schilling R, Tebruegge M, Krüger R; ptbnet TB Meningitis Study Group. Treatment and Outcome in Children With Tuberculous Meningitis: A Multicenter Pediatric Tuberculosis Network European Trials Group Study. Clin Infect Dis. 2022 Aug 31;75(3):372-381. doi: 10.1093/cid/ciab982. PMID: 34849642.

In der Auswertung des Managements und Outcomes der TBM derselben Kohorte zeigte sich, dass nur die Hälfte (49,1%) der 118 eingeschlossenen Kinder die Standardtherapie aus INH, RMP, PZA und EMB erhielt. Als 4. Medikament (neben INH, RMP und PZA) wurden häufig Streptomycin, Prothionamid oder Amikacin eingesetzt. Nahezu die Hälfte der Patient*innen wurden auf einer Intensivstation behandelt, mit einer medianen Aufenthaltsdauer von 10 Tagen. Von 104 Kindern der Kohorte konnten die Outcome-Parameter erhoben werden: 9,6% verstarben und weniger als die Hälfte (47,1%) erreichte eine restitutio ad integrum. Die häufigsten Langzeitfolgen waren eine Spastik einer oder mehrerer Extremitäten (19,2%), Entwicklungsverzögerungen (19,2%) und cerebrale Krampfanfälle (17,3%). In der multivariaten Analyse konnten der mikrobiologische Nachweis von *M. tuberculosis,* die Notwendigkeit einer neurochirurgischen Intervention und einer mechanischen Beatmung, die alle stellvertretend für die Schwere der Erkrankung stehen, als Risikofaktoren für einen ungünstigen Verlauf identifiziert werden. In einem relevanten Anteil wurden die aktuellen Dosisempfehlungen für die antituberkulösen sowie die anti-inflammatorischen Medikamente nicht umgesetzt und niedrigere Dosen verwendet. Dies ist für die Therapie der TBM besonders besorgniserregend, da hierbei nicht nur adäquate Serum- sondern auch Liquorspiegel erreicht werden müssen.

Zusammenfassend zeigte sich eine hohe Heterogenität sowohl in der Medikation als auch der Dosierung. Obwohl nur wenige Kinder bei Erstvorstellung ein fortgeschrittenes Erkrankungsstadium zeigten und die Studie in einem Setting mit hoher Resourcenverfügbarkeit stattfand, zeigte sich eine hohe Morbidität und Mortalität. Es konnten einige Risikofaktoren für ein schlechtes Outcome identifiziert werden, welche die Prognoseeinschätzung von Kindern mit TBM unterstützen können.

Thee, S., Basu Roy, R., Blázquez-Gamero, D., Falcón-Neyra, L., Neth, O., Noguera-Julian, A., Lillo, C., Galli, L., Venturini, E., Buonsenso, D., Götzinger, F., Martinez-Alier, N., Velizarova, S., Brinkmann, F., Welch, S. B., Tsolia, M., Santiago-Garcia, B., Schilling, R., Tebruegge, M., Krüger, R., … ptbnet TB Meningitis Study Group (2022). Treatment and Outcome in Children With Tuberculous Meningitis: A Multicenter Pediatric Tuberculosis Network European Trials Group Study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, *75*(3), 372–381. https://doi.org/10.1093/cid/ciab982

4 Diskussion

Auch 140 Jahre nach der Entdeckung von *M. tuberculosis* durch Robert Koch ist TB die weltweit häufigste zum Tode führende bakterielle Infektionskrankheit. Um das ambitionierte Ziel einer TB-Elimination zu erreichen, müssen auch Niedriginzidenzländer ihren Beitrag leisten.

Kinder werden meist von Erwachsenen infiziert und haben ein hohes Risiko für schwere Verlaufsformen. Eine effiziente Umgebungsuntersuchung mit besonderem Augenmerk auf Kinder ist bei Detektion eines Erwachsenen mit TB essentiell (60). Des Weiteren bedarf es einer Optimierung von Screening, Diagnose, Therapie und Managements von Kindern mit TB - nicht nur, um die mit TB assoziierte Morbidität und Mortalität bei Kindern zu minimieren, sondern auch, um die Krankheitslast für die Zukunft zu reduzieren.

Hierbei sind vor allem Risikogruppen wie Flüchtlinge in den Fokus zu nehmen. In unserer Arbeit an einer Kohorte minderjähriger, unbegleiteter Flüchtlinge konnten wir zeigen, dass nicht nur Kinder- und Jugendliche auch Hochinzidenzländern, sondern auch Minderjährige aus Ländern mit niedrigeren Inzidenzen zu einem hohen Anteil mit *M. tuberculosis* infiziert waren. Einflussfaktoren wie der Zugang zu Gesundheitssystemen, Versorgung mit Nahrungsmitteln, Massenunterkünfte sowie Dauer und Route der Flucht führen dazu, dass die TB-Inzidenzen bei Flüchtlingen dramatisch über denen im Heimatland liegen können (61-63). In Niedriginzidenzländern sind die meisten Fälle einer Folge einer Progression einer länger bestehenden LTBI, so dass sich Präventionsstrategien auf die frühe Detektion und Therapie der LTBI fokussieren sollten (64). Für Kinder liegt das Progressionsrisiko zu einer TB deutlich höher als bei Erwachsenen. Die 2-Jahresinzidenz für eine TB nach einem positiven immunologischen Test lag in einer aktuellen Meta-Analyse bei Kindern unter 5 Jahren bei 19% bei älteren Kindern von 5-19 Jahren bei 8,8-10,6% (65). In einem nationalen Konsensus Papier wird daher bei allen asylsuchenden Kindern <15 Jahren unabhängig von der Inzidenz des Herkunftslandes ein TB-Screening empfohlen (66). Im Gegensatz dazu empfiehlt das „European Centre for Disease Prevention and Control“ (ECDC), allen aus Hochinzidenz-Ländern neu ankommenden Migranten ein LTBI-Screening anzubieten, eine Alterstratifizierung ist nicht erwähnt (67). In einer aktuellen Umfrage gaben nur 15 von 30 TB Experten aus 30 Ländern an, dass in ihrem Land ein LTBI-Screening durchgeführt wird. Als Grund für ein nicht-vorhandenes Screeningprogramm wurden u.a. fehlende Daten für eine Kosteneffektivität des Screenings angegeben (68). In einer Modell-basierten Kosten-

Effektivitäts-Analyse wurde berechnet, dass ein LTBI-Screening in Deutschland für Migranten aus Gebieten mit einer TB-Inzidenz von mehr als 100/100.000 kosteneffizient ist, wobei für die Berechnung nur Daten von Personen mit einem Alter über 15 Jahren einbezogen wurden (69). Dass ein Schul-basiertes LTBI-Screening auch für Kinder kosteneffizient ist, konnte in einer Studie aus der Schweiz gezeigt werden. Dabei lag der Kosteneffizienzrechnung eine sehr konservative Schätzung mit einer LTBI-Prävalenz von 14% und einem Progressionsrisiko zu einer „aktiven" TB von 5% zu Grunde (70). Weitere Daten zur Effektivität und Kosteneffizienz eines LTBI-Screenings insbesondere bei Kindern sind notwendig, um im Rahmen anhaltender Krisen und Flüchtlingsströme eine europaweite Harmonisierung der Screening-Programme in Niedriginzidenzländern und damit einen Zusammenschluss der Länder im Kampf gegen TB zu erreichen.

Nicht nur im Rahmen eines Screening-Programms stellt sich die Frage nach der optimalen Diagnostik einer TB. Zum Nachweis einer Infektion mit *M. tuberculosis* stehen die IGRA-Tests sowie der THT zur Verfügung. Die genaue Sensitivität und Spezifität dieser Tests bei Kindern zu bestimmen ist herausfordernd. Zunächst erfolgte die Validierung bei Kindern, bei denen die Erreger in der Kultur nachgewiesen wurden, womit eine TB zweifelsfrei belegt war. Allerdings handelt es sich bei Kindern mit kulturellem Nachweis meist auch um Kinder, die schwerer erkrankt sind. Eine schwere Erkrankung kann zu einer Immunsuppression und damit einer verminderten Sensitivität dieser immunologischen Tests führen (71). Bei mild erkrankten Kindern kann die TB meist nicht mikrobiell bestätigt werden, so dass der Beweis für die Infektion mit *M. tuberculosis*, der für die Testvalidierung notwendig wäre, nicht erbracht werden kann. Zusätzlich scheint die IFN-gamma-Produktion altersabhängig zu sein, da „indeterminate results" oder falsch-negative Ergebnisse mit jungem Alter assoziiert sind bei gleichzeitig erhöhtem Risiko für eine Progression der Erkrankung (72). Aktuelle Untersuchungen eines TB-Screenings an Kindern in Kalifornien (Niedriginzidenzland) zeigten eine höhere Sensitivität der IGRAs im Vergleich zum THT bei Kindern ab einem Alter von 5 Jahren (96% versus 83%). Im Alter von 2-4 Jahren hatte beide Tests eine hohe Sensitivität von 91%, während bei Kindern unter 2 Jahren die Sensitivität für beide Tests vermindert war (IGRA 80%, THT 87%). Eine Kombination beider Tests in dieser Altersgruppe erhöhte die Sensitivität nicht (72). In unserer Umfrage zum Management der LTBI im deutschsprachigen Raum konnten wir zeigen, dass mehr als die Hälfte der Befragten für Kinder <5 Jahren eine andere Herangehensweise als bei älteren Kindern wählen. In dieser Altersklasse werden die beiden

immunologischen Tests meist kombiniert angewendet sowie bereits initial ein Röntgen-Thorax veranlasst (73).

Im Rahmen einer europaweiten multizentrischen Beobachtungsstudie, konnten wir erstmalig die Anwendung der immunologischen Tests auch bei Kindern mit einer schweren TB -einer TBM- in der klinischen Routine in Niedriginzidenzländern evaluieren (74). Allein angewendet hatten die immunologischen Tests eine Sensitivität von 50% (THT mit einem cut-off von 10mm) bis 82,5% (T-SPOT.TB®), so dass bei Anwendung nur eines Tests bei mindestens jedem 5. Kind eine falsch negatives Testergebnis vorläge. Bei Präsentation in einem fortgeschrittenen Stadium der TBM trat ein falsch negatives Ergebnis dabei häufiger auf als in frühen Stadien. In Kombination aller zur Verfügung stehenden immunologischen, kulturellen oder molekularen diagnostischen Tests, zeigte sich bei 84,4% der Kinder mit TBM zumindest in einem der Tests ein positives Ergebnis. Aktuell liegt kein Diagnostikum vor, dass eine höhere Sensitivität als bisherige Untersuchungsmethoden hat. Die Anwendung der IGRA-Tests aus Liquor bei TBM zeigte in einer Meta-Analyse eine Sensitivität von 77% und war in einer weiteren Studie dem Blut-IGRA-Test überlegen (75, 76). Dort, wo ein serologischer IGRA-Test bereits etabliert ist, kann dieser Test möglicherweise mit einem geringen labortechnischen Aufwand zu einer erhöhten Sensitivität beitragen (76). Dennoch gab keiner der Teilnehmer unserer Studie zur TBM an, einen IGRA-Test aus Liquor durchzuführen. Im Gegensatz zu Hochinzidenzländern stehen in Niedriginzidenzländern regelhaft molekulare Testverfahren zur Verfügung, bei denen es sich jedoch oft um „in-house“- oder kommerzielle PCR-Verfahren handelt, die eine Vergleichbarkeit der Sensitivität erschweren. Gut validiert ist Xpert MTB/RIF Ultra assay®, der bei Erwachsenen mit TBM eine Sensitivität von über 70%, bei Kindern allerdings von nur 50% aufweist (77, 78). Ein großer Vorteil des Xpert MTB/RIF Ultra assays® ist die gleichzeitige Bestimmung einer RMP-Resistenz, deren Ergebnis innerhalb eines Tages vorliegt.

Zusätzlich zur immunologischen Testung sind klinische und radiologische Parameter für die Diagnosestellung einer TBM bedeutend. Die in unserer Kohorte am häufigsten aufgetretenen Symptome wie Fieber, Erbrechen, Kopfschmerzen und Bewusstseinsminderung sind dabei unspezifisch. Auch das zur Harmonisierung klinischer Studien entworfene Punktesystem UTRCD (Uniform TBM Research Case Definition), welches klinische Kriterien, Liquorbefunde, cerebrale Bildgebung und Hinweise auf eine TB in einem anderen Organsystem umfasst (79), zeigte eine suboptimale Sensitivität in unserer Kohorte. Unterstützend für die Diagnose einer TBM war ein Röntgen-Thorax, in dem etwa drei Viertel der Kinder unserer Kohorte TB-

verdächtige Veränderungen aufwies. Die Häufigkeit von TB-typischen pulmonalen Veränderungen in der Bildgebung variiert zwischen den Studien. Während in einer südafrikanischen Studie an Kindern mit TBM weniger als die Hälfte der Kinder Auffälligkeiten im Röntgen-Thorax zeigte, konnten bei einer Studie an Erwachsenen in mehr als zwei Dritteln entsprechende Auffälligkeiten im CT gefunden werden (80, 81). Aufgrund der hohen Verfügbarkeit und dem wahrscheinlichen Zusatznutzen sollte bei Verdacht auf TBM auch ein Röntgen-Thorax durchgeführt werden.

In der cerebralen Bildgebung zeigten sich in unserer Kohorte bei mehr als 80% typische Veränderungen einer TBM wie Hydrocephalus, basales Enhancement und intracerebrale Tuberkulome, was Berichten aus anderen Kohorten entspricht. Die cerebrale Bildgebung ist daher ein essentieller Bestandteil in der Diagnostik einer TBM.

Nach Diagnosestellung einer LTBI oder TB wird der weitere Verlauf maßgeblich durch die durchgeführte Therapie bestimmt. Durch geringe Fallzahlen besteht in Niedriginzidenzländern die Gefahr, dass sowohl das Wissen als auch die Erfahrung in der Behandlung der kindlichen TB abnimmt. Wir konnten zeigen, dass auch unter Kinderpneumologen und Infektiologen mehr als 40% der Befragten weniger als 10 Kinder pro Jahr bezüglich einer TB evaluieren. Die Befragung ergab, dass als Chemoprävention hauptsächlich eine INH-Monotherapie für bis zu 9 Monaten verwendet wurde und nur etwa ein Drittel gab an, eine Kombinationstherapie aus RMP und INH zu verwenden. Rifamycin-basierte Therapien sind der INH-Monotherapie vorzuziehen, da sie eine kürzere Dauer haben bei einer vergleichbaren oder sogar besseren Effektivität als eine INH-Monotherapie, wodurch ein deutlich höherer Anteil der Patient*innen die Therapie komplettiert (82). Die Verträglichkeit der Kombinationstherapie bei Kindern und Jugendlichen ist sehr gut, wie wir auch in eigenen Arbeiten zeigen konnten (83, 84). Dennoch bleibt die Therapieadhärenz herausfordernd, unter anderem, weil die Patient*innen mit LTBI keine TB-spezifischen Symptome verspüren. In unserer Berliner Kohorte an minderjährigen Flüchtlingen, die eine Chemoprävention erhielten, bestand bei etwa einem Viertel der Verdacht auf eine Nicht-Adhärenz. Kürzere und einfachere Therapien sind dringend notwendig. Die Einnahme von Rifapentin und INH einmal pro Woche über 12 Wochen hat sich als gleichwertige und sichere LTBI-Therapie erwiesen und ein kürzeres Regime mit täglicher Gabe von INH und Rifapentin für nur 30 Tage stellt eine vielversprechende Alternative dar (85, 86). In einer Studie an Kindern und Jugendlichen zwischen 2-19 Jahren, komplettierten 385 (94%) von 408 Teilnehmenden die einmonatige

Chemoprävention mit INH und Rifapentin; die Therapie zeigte eine hohe Effizienz, Nebenwirkungen traten nur bei einem Patienten auf, welcher Dysästhesien entwickelte, aufgrund derer die Therapie beendet wurde (87). Kürzlich konnte in einem Makakenaffen-Modell gezeigt werden, dass INH/Rifapentin nicht nur sich replizierende, sondern auch in Lymphknoten persistierende *M. tuberculosis* abtötet, was einen bedeutenden Schritt für eine Elimination der TB weltweit darstellt (88). Es ist daher unverständlich, dass Rifapentin, welches von der US Food and Drug Association (FDA) bereits im Jahr 1998 zugelassen wurde, in den meisten Europäischen Ländern nicht verfügbar ist (89).

Für eine effektive Therapie ist die ausreichende Dosierung der verwendeten Medikamente essentiell. Wir konnten bereits sehr früh für RMP zeigen, dass Kinder im Vergleich zu Erwachsenen deutlich höhere Dosierungen (bezogen auf mg/kg KG) benötigen, um Serumspiegel zu erreichen, deren Effektivität in Studien an Erwachsenen gut belegt sind. Es konnte gezeigt werden, dass sowohl die Aktivität gegenüber *M. tuberculosis* als auch die Entwicklung einer RMP-Resistenz konzentrationsabhängig ist, weswegen Dosen bis 35mg/kg KG bei Erwachsenen und auch Kindern evaluiert wurden (90, 91). Pharmakokinetische Modellierungsstudien haben ebenfalls ergeben, dass bei Kindern höhere RMP-Dosierungen als 30mg/kg KG notwendig sein könnten (92). In einer kürzlich publizierten Pharmakokinetik-Sicherheitsstudie an Kindern wurden RMP-Dosen bis 75mg/kg KG/Tag über einen kurzen Zeitraum evaluiert. Als Zielspiegel wurde ein RMP-Serumspiegel definiert, der denen von Erwachsenen nach einer Dosis von 35mg/kg KG entsprach, da sich dieser in einer vorangegangen Studie als sehr effizient und sicher zeigte (90). Um entsprechende Serumspiegel zu erreichen, waren bei Kindern Dosen bis 65-70mg/kg notwendig. Nebenwirkungen traten in etwa der Hälfte der Teilnehmer auf, betrafen vor allem den Gastrointestinaltrakt und waren mild (Toxizität Grad 1 oder 2) (91). Nur bei 2 Kindern wurde die Studie aufgrund gastrointestinaler Nebenwirkungen abgebrochen, Hinweise für eine Hepatotoxizität ergaben sich nicht. In einer vorangegangenen Übersichtsarbeit wurde ebenfalls zusammenfassend festgestellt, dass eine schwere RMP-induzierte Hepatotoxizität bei Kindern sehr selten und nicht Dosis-abhängig ist (93).

In anschließenden pharmakokinetischen Studien konnten wir zeigen, dass für Kinder nicht nur bei weiteren Erstrangmedikamenten, sondern auch bei Zweitrangmedikamenten höhere Dosen der antituberkulösen Medikamente benötigt werden (54, 56, 94-99). In Folge weiterer Evidenz wurden im Jahr 2014 die WHO-Dosisempfehlungen angepasst (59). Wir konnten

zeigen, dass die Umsetzung dieser Dosisempfehlungen sowohl bei der Therapie der LTBI als auch der Therapie der TBM bei einem relevanten Anteil nicht erfolgt ist. Dies ist insbesondere für die Therapie der TBM besorgniserregend, bei der nicht nur adäquate Serum- sondern auch Liquorspiegel erreicht werden müssen. RMP hat eine geringe Liquorgängigkeit, sobald sich die Inflammation der Blut-Hirn-Schranke gelegt hat, wobei die RMP-Konzentration im Liquor mit höherer Dosis ansteigt (100). Die kürzlich aktualisierten WHO-Leitlinie zur Therapie von Kindern mit TBM trägt dem Rechnung und es wird nun auch ein intensiviertes Therapieregime mit den Dosisempfehlungen von INH (20mg/kg), RMP (20mg/kg), PZA (40mg/kg) und Ethionamide (20mg/kg) als gleichwertige Alternative zur vormaligen Standardtherapie aufgeführt (38). Bei Erwachsenen mit TBM konnte gezeigt werden, dass noch höhere RMP-Dosen bis 35mg/kg mit einem Überlebensvorteil assoziiert sind (101, 102). In einer kürzlich publizierten Studie an Kindern und Jugendlichen mit TBM wurden ebenfalls höhere RMP-Dosen (30mg/kg) sowie die Gabe von Levofloxacin im Vergleich zur Standardtherapie untersucht (103). Während die Gabe von Levofloxacin zu keiner Verbesserung des Outcomes führte, zeigte sich bei den Kindern mit höherer RMP-Dosierung ein statistisch signifikant besseres neurokognitives Outcome bei allerdings erhöhter Rate an Nebenwirkungen (103). In einer laufenden Studie an geplant 400 Kindern mit TBM (Einschluss bis 2023) wird die Anwendung eines intensivierten Regimes (RMP 30 mg/kg, INH 20 mg/kg, PZA 40 mg/kg und Levofloxazin 20 mg/kg) für 6 Monate im Vergleich zu der Standardtherapie über 12 Monate verglichen. Zusätzlich werden die Teilnehmer bezüglich des Erhalts einer anti-inflammatorischen Therapie mit Aspirin randomisiert (SURE:http://www.isrctn.com/ISRCTN40829906).

Bei der Wahl des 4. Medikaments neben INH, RMP und PZA in der Mehrfachtherapie der TBM sollten die erreichbaren Liquorkonzentrationen der Substanz unbedingt in Betracht gezogen werden. Die Liquorgängigkeit von EMB ist nur gering. Deutlich besser ist die Liquorgängigkeit von Ethionamid, so dass dessen Anwendung Eingang in die aktuelle WHO-Therapieempfehlung gefunden hat. Ein weiterer Vorteil von Ethionamid ist, dass dieses auch bei Vorliegen einer INH-monoresistenter TBM durch eine *katG*-Mutation wirksam ist. Allerdings wird die Anwendung durch Hepatotoxizität, gastrointestinale Nebenwirkungen und die Assoziation mit einer Hypothyreose eingeschränkt, wie wir auch an einer Kohorte von Kindern mit multiresistenter TB zeigen konnten (94, 104, 105). Im deutschsprachigen Raum steht Prothionamid, das Propyl-Analog des Ethionamids, als gleichwertige Alternative zur

Verfügung. Ebenfalls gut liquorgängig und in der Therapie der TBM angewandt, sind Chinolone. Der Vorteil der Chinolone (v.a. Levofloxacin und Moxifloxacin) ist die deutlich bessere Verträglichkeit im Vergleich zu Ethionamid (106). Als weitere mögliche Alternative steht Linezolid zur Verfügung, welches bislang nur an Erwachsenen mit TBM untersucht wird (SIMPLE study: NCT03537495, Laser-TBM: NCT03927313, ALTER: NCT04021121, INTENSE-TBM: NCT04145258). Die Ergebnisse dieser Studien sind essentiell, um Therapieregime auch bei Kindern mit TBM zu optimieren und evidenzbasiert anzuwenden. Das bislang unzureichende Vorliegen randomisierter Studien in der Therapie der TBM bei Kindern spiegelt sich auch in der hohen Heterogenität der Medikamentenkombinationen wider, die wir für den europäischen Raum zeigen konnten.

Das hohe Morbiditätsrisiko bei TBM wird neben der direkten Pathogenität von *M. tuberculosis* durch eine dysregulierte Immunantwort bedingt (107). In einem Cochrane Review zeigte sich, dass der Einsatz von Glucokorticoiden mit einer reduzierten Mortalität bei TBM assoziiert ist (108). Wie auch für die antituberkulöse Therapie konnten wir in unserer Studie eine häufige Unterdosierung der anti-inflammatorischen Medikamente in unserer Kohorte dokumentieren. Weitere anti-inflammatorische Therapien mit Aspirin, TNF-alpha-Inhibitoren wie Thalidomid oder Anti-TNF-alpha-Antikörpern wie Infliximab oder Adalimumab wurden in kleinen Kohorten evaluiert und zeigten positive Effekte, größere Studien fehlen bislang (109, 110). Wir konnten zeigen, dass auch in Niedriginzidenzländern mit hoher Verfügbarkeit diagnostischer, medikamentöser, intensivmedizinischer und neurochirurgischer Interventionsmöglichkeiten die Morbidität der TBM bei Kindern hoch ist. Obwohl sich in unserer Kohorte weniger als 10% der Kinder mit einer schweren Form der TBM präsentierten, erlangten weniger als die Hälfte am Ende der Therapie eine restitutio ad integrum.

Neben Intensivierung der vorab beschriebenen Maßnahmen zur Senkung der TB-Inzidenz sind die Anwendung neuer pharmakokinetisch-pharmakodynamischer Erkenntnisse und neuer Erkenntnisse aus Medikamentenstudien sowie ein multidisziplinäres Management essentiell, um eine Optimierung der Therapie der TBM zu erreichen und die Mortalität und Morbidität bei Kindern zu senken. Des Weiteren bedarf es einer kontinuierlichen Fortbildung medizinischen Personals und das Vorhandensein aktueller Leitlinien, um das Bewusstsein für die TB bei Kindern aufrechtzuerhalten. Dabei ist der Zusammenschluss mit internationalen Netzwerken wie dem ptbnet essentiell. Nur durch die Zusammenarbeit und den Austausch europäischer Zentren kann eine ausreichende Evidenz für die Diagnose und Behandlung der

TB in Niedriginzidenzländern im europäischen Setting generiert werden auf deren Basis das ehrgeizige Ziel der End-TB Strategie, TB in Niedringinzidenzländern zu eliminieren, erreicht werden kann.

5 Zusammenfassung

Im Rahmen der ambitionierten „End TB strategy“ der Weltgesundheitsorganisation (WHO) wurde für Niedriginzidenzländer das Ziel definiert, eine Elimination der TB als Gesundheitsproblem bis zum Jahr 2050 zu erreichen. Ein wichtiger Bestandteil einer erfolgreichen TB-Kontrolle ist dabei nicht nur die Identifikation von Risikogruppen, sondern auch die Diagnose und Behandlung der LTBI sowie die optimierte Therapie der manifesten TB. Kinder stellen eine besonders vulnerable Gruppe für TB dar, da sie im Vergleich zu Erwachsenen ein erhöhtes Risiko für schwere, disseminierte Verläufe wie eine TBM haben.

Wir konnten zeigen, dass ein Screening auf TB mit einem IGRA-Test bei unbegleiteten minderjährigen Flüchtlingen auch bei großen Flüchtlingszahlen durchführbar ist und dass nicht nur Kinder- und Jugendliche aus Hochinzidenzländern, sondern auch aus Ländern mit niedriger TB-Inzidenz aufgrund der Bedingungen während der Flucht und bei Unterbringung in Massenunterkünften ein hohes Risiko für eine TB-Infektion aufweisen. Die Flüchtlinge, bei denen eine LTBI diagnostiziert wurde, erhielten eine dreimonatige Chemoprävention mit RMP und INH. Die Therapie wurde insgesamt gut vertragen, die häufigste Nebenwirkung waren transiente gastrointestinale Beschwerden. Dabei stellte sich die Versorgung einer Patientengruppe, die häufig nur temporär untergebracht ist, als herausfordernd dar. Da eine LTBI keine meldepflichtige Erkrankung ist, ist die Nachverfolgung der betroffenen Kinder und Jugendlichen zusätzlich erschwert und damit das Risiko einer nicht adäquat durchgeführten Therapie erhöht.

In einer weiteren Erhebungsstudie konnten wir zeigen, dass pädiatrische Pneumologen und Infektiologen in Deutschland, Österreich und der Schweiz meist nur wenige Kinder pro Jahr auf eine TB hin untersuchen und damit das Risiko besteht, dass das Wissen und Erfahrungen zur Diagnostik und Therapie dieser Erkrankung außerhalb von Zentren deutlich abnehmen. Dies zeigte sich zum einem in einer deutlichen Heterogenität im Management der LTBI, zum anderen in der häufigen Verwendung von langwierigen INH-Monotherapien. Kürzere Kombinationstherapien von INH und RMP sind äußerst effektiv in der Prävention einer TB und mit einer deutlich besseren Medikamentenadhärenz assoziiert als INH-Monotherapien. Eine

Therapie ohne Vorliegen von Symptomen durchzuführen, stellt eine große Herausforderung für die Patient*innen dar und es bedarf dringend der Evaluation noch kürzerer Therapien der LTBI auch bei Kindern.

Da sich die Prinzipien der Therapie der TB für Erwachsene und Kinder nicht unterscheiden, sollten bei Kindern dieselben Serumspiegel der TB-Medikamente angestrebt werden, wie die, deren Effektivität in Studien bei Erwachsenen gut belegt sind. Wir konnten in einer ersten pharmakokinetischen Studie an 27 Kindern mit pulmonaler TB im Alter von 2-14 Jahren zeigen, dass Kinder niedrigere maximale Serumspiegel und eine verminderte AUC nach einer RMP-Dosis von 10mg/kg KG aufweisen als Erwachsene nach einer RMP-Standarddosis. Für eine adäquate Therapie benötigen Kinder deutlich höhere mg/kg Dosierungen als Erwachsene, was insbesondere für schwere Erkrankungsformen der TB äußerst relevant ist.

Eine der schwersten Erkrankungsformen der TB stellt die TBM dar, für die vor allem jüngere Kinder ein hohes Risiko haben. Eine frühzeitige Diagnosestellung und Einleitung der Therapie sind maßgeblich für das spätere Outcome.

In einer ersten Arbeit im Rahmen des europäischen Netzwerkes „ptbnet“ haben wir die Anwendung immunologischer und mikrobiologischer Diagnostikverfahren bei Kindern mit TBM in Niedriginzidenzländern untersucht. Siebenundzwanzig europäische Zentren nahmen an dieser multizentrischen, retrospektiven Studie teil. Wir konnten zeigen, dass die aktuellen diagnostischen Tests in Kombination zwar bei mehr als 80% der Kinder mit TBM-Verdacht einen zusätzlichen Hinweis auf eine TB geben, bei fast 20% muss eine Therapie jedoch allein aufgrund des Verdachtes eingeleitet werden. Es bedarf daher dringend einfach anzuwendender, optimalerweise direkt verfügbarer Diagnostika, um alle Kinder mit TBM zu erfassen.

In der Auswertung des Managements und Outcomes der TBM in derselben Kohorte zeigte sich eine hohe Morbidität und Mortalität, obwohl sich nur wenige Kinder in einem fortgeschrittenen Erkrankungsstadium präsentierten. Wir konnten den mikrobiologischen Nachweis von *M. tuberculosis* sowie die Notwendigkeit einer neurochirurgischen Intervention und einer mechanischen Beatmung als Risikofaktoren für einen ungünstigen Verlauf identifizieren. Bei einem relevanten Anteil der Kinder wurden die aktuellen Dosisempfehlungen für die antituberkulösen Medikamente sowie die anti-inflammatorische Therapie nicht umgesetzt und niedrigere Dosen verwendet.

Zusammenfassend konnten wir in unseren Arbeiten zeigen, dass bei Kindern und Jugendlichen das Screening auf TB in Risikogruppen durchführbar und notwendig ist, dass die diagnostischen Möglichkeiten einer TB insbesondere für die schwere Erkrankungsform einer TBM eine unzureichende Sensitivität aufweisen und dass für das Management und Therapie der TB bei Kindern weiterhin ein Optimierungsbedarf besteht. Die konsequente Detektion von LTBI/TB im Rahmen von Umgebungsuntersuchungen und Screening von Risikogruppen sowie die Therapie der LTBI mit kürzeren, vereinfachten Therapien stellen die wichtigsten Maßnahmen in Niedriginzidenzländern dar, um das Ziel einer TB-Elimination zu erreichen. Zur Senkung der Morbidität und Mortalität schwerer Erkrankungsformen sind die Generierung und Anwendung weiterer Evidenz aus Therapiestudien zur Optimierung der Versorgung essentiell. In Niedriginzidenzländern ist das Risiko für eine abnehmende Expertise hoch und es bedarf Maßnahmen wie kontinuierlicher Fortbildungsangebote und aktueller Leitlinien, um das Bewusstsein für das Vorhandensein von TB bei Kindern zu verbessern. Die Zusammenarbeit und der Austausch in Netzwerken wie beispielsweise dem ptbnet tragen hierzu maßgeblich bei.

6 Literaturangaben

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Erklärung

§ 4 Abs. 3 (k) der HabOMed der Charité

Hiermit erkläre ich, dass

- weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wurde,
- die vorgelegte Habilitationsschrift ohne fremde Hilfe verfasst, die beschriebenen Ergebnisse selbst gewonnen sowie die verwendeten Hilfsmittel, die Zusammenarbeit mit anderen Wissenschaftlern/Wissenschaftlerinnen und mit technischen Hilfskräften sowie die verwendete Literatur vollständig in der Habilitationsschrift angegeben wurden,
- mir die geltende Habilitationsordnung bekannt ist.

Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

Berlin, 08. November 2022