



Correlazione tra TB e Malnutrizione Acuta Severa nei pazienti pediatrici

Esperienza condotta in un reparto pediatrico di un ospedale rurale Tanzaniano in collaborazione con Medici Con l'Africa CUAMM

Ferrara, 18/11/2016

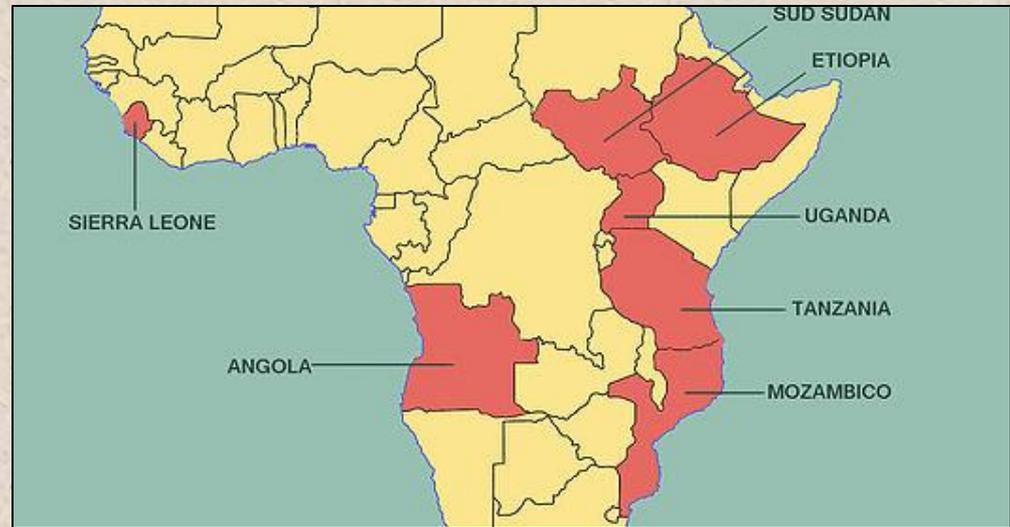
Martina Mazzocco

Cos'è il CUAMM?

Medici con l'Africa Cuamm è la prima organizzazione non governativa sanitaria italiana, che si spende per la promozione e la tutela della **salute delle popolazioni africane.**

A tale scopo si impegna **nella formazione** delle risorse umane dedicate e **nell'affermazione del diritto umano fondamentale della salute per tutti.**

Dove?



La mia esperienza da JPO



Tosamaganga

Qualche dato..



53.470.000	Popolazione	59.798.000
60/64 anni	Aspettativa di vita m/f	80/85 anni
17,5 anni	Età media della popolazione	44,3 anni
2.742	PIL (PPA)/anno (USD)	35.131
5,3%	Prevalenza di HIV+ nella popolazione adulta tra i 15 e i 49 anni	no data
5,2	Tasso totale di fertilità/per donna	1,5
18,8	Tasso di mortalità neonatale / 1000 nati vivi	2,1
398	Mortalità materna /100.000 nati vivi	4
3	Personale medico/100.000 abitanti	376

MALNUTRITION IN NUMBERS



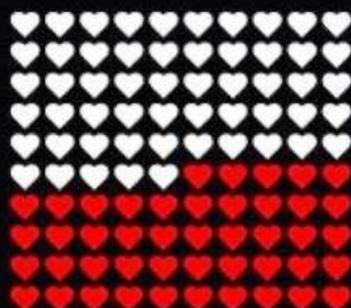
WORLD



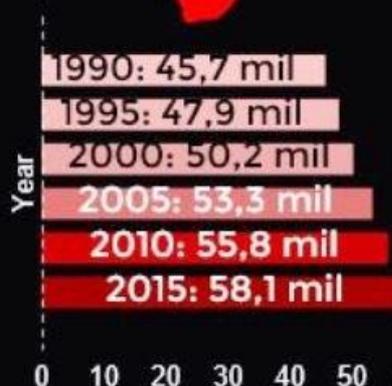
AFRICA



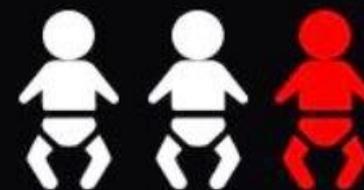
TANZANIA



Every 100 children's deaths,
45 ARE RELATED TO MALNUTRITION



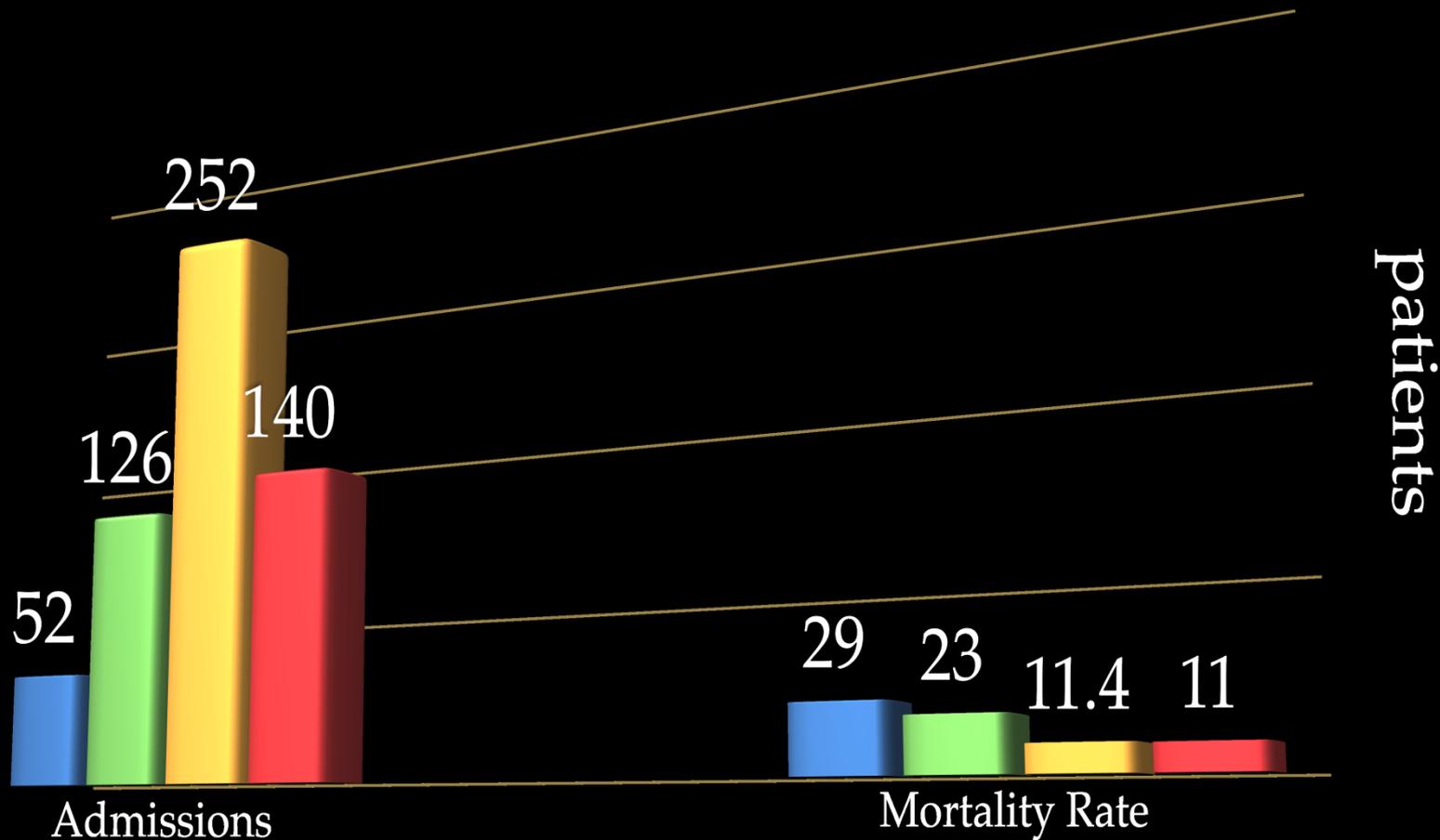
The number of malnourished children
IS INCREASING



1/3 of under-5 children
is malnourished
(3.000.000 children)

In particolare nella regione di Iringa la prevalenza di malnutrizione cronica nella popolazione sotto i 5 anni è 44,2%. Circa 2000 bambini sono invece colpiti dalla malnutrizione acuta severa.

Qualche dato (2013-2016)



LA MALNUTRIZIONE

L'Organizzazione Mondiale della Sanità (OMS) definisce la malnutrizione come lo squilibrio cellulare tra apporto di nutrienti e di energia, e la quantità di questi necessaria al corpo per garantire la crescita, la manutenzione, e le funzioni specifiche dell'organismo.



La malnutrizione cronica o stunting

Diagnosi basata sul mancato raggiungimento degli standard di altezza per età, fissati dalla WHO.



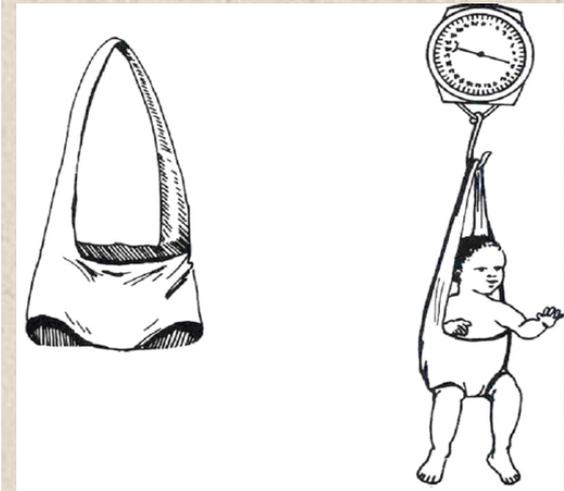
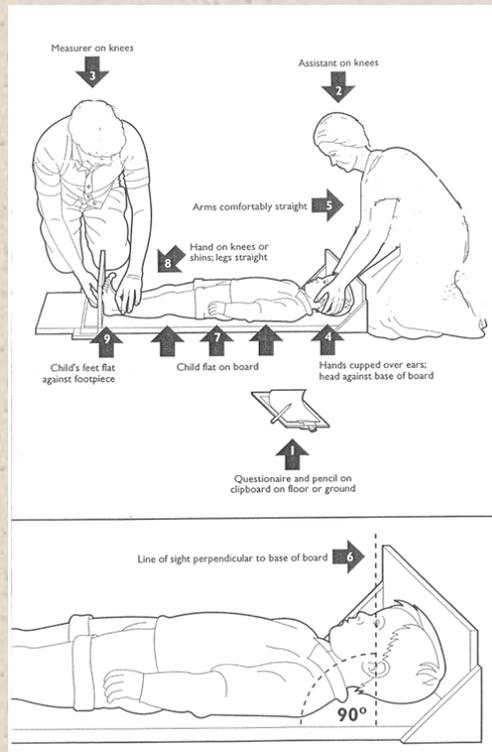
La malnutrizione acuta o wasting

Si sviluppa come risultato di una rapida perdita di peso o incapacità ad acquisire peso.

LA MALNUTRIZIONE ACUTA

Può essere **moderata (MAM)** o **grave (SAM)**.

Essa viene misurata nei bambini attraverso l'indice nutrizionale dato dal rapporto peso/altezza o con la misura della circonferenza brachiale MUAC.

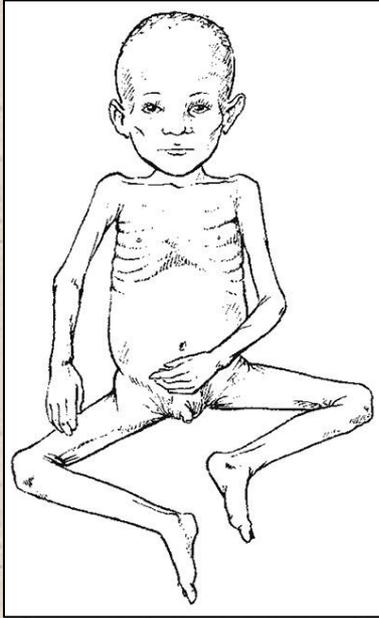


CRITERI PER LA DIAGNOSI DI SAM

- Presenza di edema improntabile
- Peso per Lunghezza/Altezza < -3 DS
- Circonferenza brachiale (MUAC) < 115 mm



Marasma



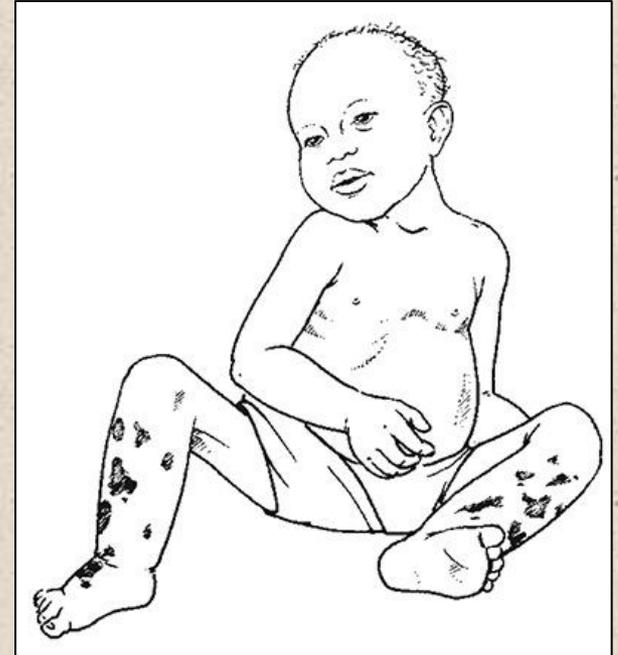
Caratterizzato dal deperimento della massa muscolare e la deplezione dei depositi di grasso corporeo.

E' causato da un inadeguato intake di tutti i nutrienti ma specialmente delle fonti di energia (calorie totali)



Kwashiorkor

Caratterizzato dalla presenza di edema periferico, fondamentale per stabilirne la diagnosi.



PATOGENESI DEL KWASHIORKOR

1° IPOTESI

Nel passato si pensava che il fattore chiave alla base dello sviluppo dell'edema fosse un deficit proteico



Assunzione di nutrienti inadeguati per la sintesi proteica



Ipoalbuminemia (riscontrata in molti pz con K)

Supporto a tale ipotesi: la concentrazione di albumina generalmente aumentava dopo le prime due settimane di refeeding.

MA

Diverse evidenze hanno mostrato che la deficienza di intake proteico NON è il trigger primario:

- Gruppi di pz con K ma senza ipoalbuminemia
- Sviluppo di K nonostante un'adeguata proporzione di proteine nella dieta
- Guarigione dal K con supportive care anche senza cambiare il contenuto proteico della dieta
- Assenza di K in modelli animali alimentati con dieta a basso contenuto proteico

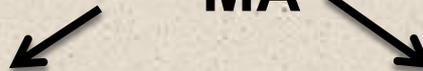
2° ipotesi:

Eccesso di radicali liberi che potrebbero contribuire all'edema e all'infiammazione danneggiando le membrane cellulari

A supporto di tale ipotesi:

- Riscontro di ridotti di Glutathione nel sangue dei pz con K (ma non nei casi con marasma)
- Deficit di altri scavenger di radicali liberi

MA



Alcuni piccoli trials hanno confermato tale Hp

Un grande trial è giunto alla conclusione che la deplezione di antiossidanti potrebbe essere una conseguenza piuttosto che una causa di K

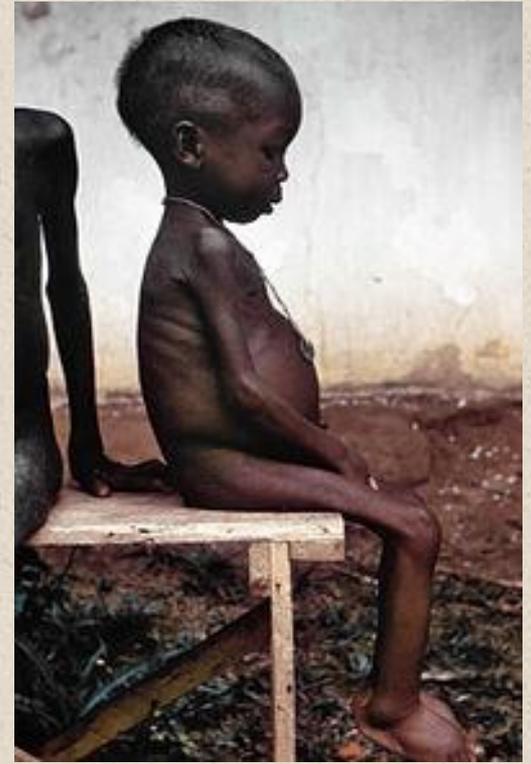
3° ipotesi:

Vi è inoltre evidenza che il K sia associato ad alterazioni del **microbioma intestinale**, ma non è chiaro se questo partecipi alla patogenesi del K o sia secondario all'effetto di fattori enzimatici e immunologici nei bambini malnutriti.

Marasma- Kwashiorkor

Si manifesta in bambini che hanno un inadeguato intake dietetico di tutti i nutrienti ed è scatenato da una comune infezione dell'infanzia.

Questa forma è frequentemente associata ad una morbidità ed una mortalità più elevata.

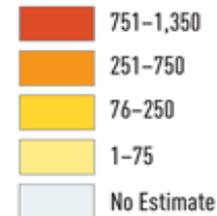


Geografia della Tuberculosis

Of the nearly nine million annual tuberculosis diagnoses, one quarter occur in Africa, with approximately **530,000 in children**

According to the Global TB report of 2011, Tanzania ranks at **number 20 among 22 high TB burden countries**. Childhood TB contributes about 10% of all notified cases in Tanzania.

Rate per 100,000 Population



Tubercolosi in età pediatrica

- Alto rischio che l'infezione si trasformi in malattia nei soggetti di età nei soggetti di età < 5 aa e durante l'adolescenza
- Maggiore probabilità di sviluppare forme extrapolmonari e forme disseminate gravi
- Caratteristica peculiare del bambino è che è molto recettivo e paucibacillifero



Clinica

- Febbre (serotina)
- Tosse (secca e irritativa)
- Inappetenza
- Astenia - adinamia
- Sudorazione
- Calo ponderale
- Sintomatologia dolorosa (scheletro)



La diagnosi nei bambini è molto difficile

- La TBC mima molte malattie comuni dell'infanzia (febbre, tosse)
- Mancanza di un "gold standard" per la diagnosi
- Bassa carica batterica ("natura paucibacillare")
- Incapacità del bambino piccolo ad espettorare



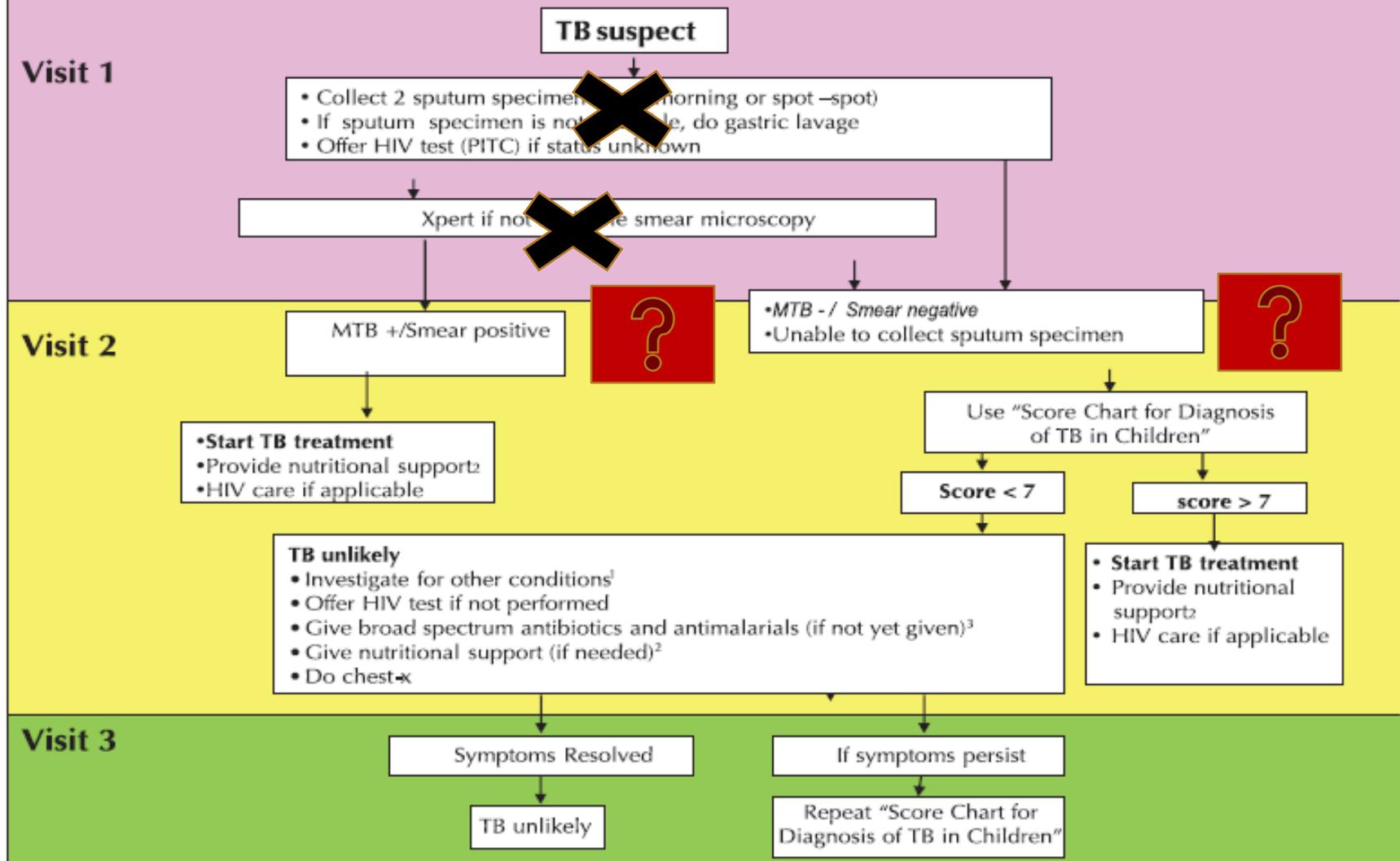
“Tra i pazienti al di sotto dei 15 anni, solo il 2% di tutti i casi riportati, ha avuto la conferma batteriologica”

Report del 2011 della Tb in Tanzania



ALGORITHM FOR DIAGNOSING PULMONARY TB IN CHILDREN BELOW 6 YEARS OLD

Algorithm for Diagnosing Pulmonary TB in Children below 6 years old



	0	1	2	3	4	Score
General features						
Duration of Illness	Less than 2 weeks	2-4 weeks		More than 4 weeks		
Failure to thrive or weight loss	Weight gain	No weight gain or weight faltering		Weight loss		
TB contact	None	Reported (but no documentation) smear negative or EPTB		Smear positive (with documentation)		
TST	Negative, not done			Positive		
Malnutrition not improved after four weeks of therapy				Present		
Unexplained fever not responding to appropriate therapy			Positive			
Local features						
Chest x-ray				TB-suggestive features like infiltration, cavity, or hilar lymph nodes		
Painless, enlarged lymph nodes		Any, non-cervical lymph nodes		Positive cervical lymph nodes		
Swelling of bones or joint				Positive		
Unexplained ascites or abdominal mass				Positive		
Central nervous system findings: meningitis, lethargy, irritability and other behaviour changes				Positive		
Angle deformity of the spine					Positive	
TOTAL SCORE: A score of 7 or more indicates a high likelihood of TB. Refer the child for TB treatment.						

What are the performance characteristics of clinical scoring systems for TB in SAM and/or HIV positive children?

A recent systematic review on clinical scoring systems for diagnosis of TB in children found a number of different systems, but no studies focussed on children with SAM, or compared validity of systems between SAM and well-nourished children.⁵¹ In part this is because acute malnutrition itself (especially if unresponsive to nutritional rehabilitation) is a criterion in many of the scoring systems. In cases of TB where acute malnutrition is a more prominent feature than cough, for example, it is also less likely that suitable specimens for gold-standard diagnosis will be available. Our approach (in line with WHO) is to consider

GENEXPERT

GeneXpert è un sistema integrato che automatizza i tre processi necessari per eseguire una reazione di Real-Time PCR:

- preparazione del campione
- amplificazione
- rilevamento della sequenza target.



Il sistema permette il rilevamento di **MTBC** in campioni clinici e il contemporaneo **evidenziamento di mutazioni associate a rifampicina-resistenza.**

Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults

2014

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Main results

We included 27 unique studies (integrating nine new studies) involving 9557 participants. Sixteen studies (59%) were performed in low- or middle-income countries. For all QUADAS-2 domains, most studies were at low risk of bias and low concern regarding applicability.

As an initial test replacing smear microscopy, Xpert® MTB/RIF pooled sensitivity was 89% [95% Credible Interval (CrI) 85% to 92%] and pooled specificity 99% (95% CrI 98% to 99%), (22 studies, 8998 participants: 2953 confirmed TB, 6045 non-TB).

As an add-on test following a negative smear microscopy result, Xpert®MTB/RIF pooled sensitivity was 67% (95% CrI 60% to 74%) and pooled specificity 99% (95% CrI 98% to 99%; 21 studies, 6950 participants).

For smear-positive, culture-positive TB, Xpert® MTB/RIF pooled sensitivity was 98% (95% CrI 97% to 99%; 21 studies, 1936 participants).

For people with HIV infection, Xpert® MTB/RIF pooled sensitivity was 79% (95% CrI 70% to 86%; 7 studies, 1789 participants), and for people without HIV infection, it was 86% (95% CrI 76% to 92%; 7 studies, 1470 participants).

ADULTS

Increased MTB/RIF A Prospe

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Background. Dia
and reliable tests, es
evaluate the diagnos
in a high tuberculos

Methods. In a p

tuberculosis were assigned to predefined diagnostic subgroups, based on microbiological and clinical findings. Results of smear microscopy and culture were compared against diagnostic performance of Xpert.

Results. Twenty-eight of 164 children (17.1%) had confirmed tuberculosis. Xpert detected 100% (95% confidence interval [CI], 59.0%–100%) of smear-positive cases and 66.6% (95% CI, 43.0%–85.4%) of culture-positive but smear-negative cases. In the per-sample analysis, Xpert displayed a similar sensitivity (54.7% [95% CI, 42.7%–66.2%]) compared with culture methods. Xpert detected 3-fold more confirmed tuberculosis cases than smear microscopy but with equal rapidity. Four additional cases (8.5%) with clinical tuberculosis but negative culture were diagnosed by Xpert. Testing second and third samples increased sensitivity by 20% and an additional 16%, respectively. When tuberculosis was reliably excluded, Xpert's specificity was 100%. HIV infection did not affect diagnostic accuracy of Xpert.

Conclusions. Xpert was easy to perform and displayed similar diagnostic accuracy as culture methods in children with suspected tuberculosis. Rapid turnaround times should reduce treatment delay and improve patient outcome, although sensitivity remains suboptimal and access is dependent on local laboratory infrastructure.

Using Xpert MTB/RIF to diagnose pulmonary TB and rifampicin resistance in children

A total of 16 studies (12 published, 4 unpublished) were included in the review. All studies were performed at higher levels of care, and the children included in the studies were mainly inpatients.

The diagnosis of pulmonary TB was evaluated in 13 studies that included 2603 participants. The overall pooled sensitivity of Xpert MTB/RIF compared against culture as the reference standard in children suspected of having TB was 66% (95% CrI, 52-77%) in 10 studies where expectorated sputum or induced sputum was used; the pooled sensitivity was 66% (95% CrI, 51-81%) in 7 studies where gastric lavage aspirates were used. The pooled specificity of Xpert MTB/RIF compared against culture as the reference standard was at least 98% with narrow confidence intervals. The pooled sensitivity of Xpert MTB/RIF in specimens from culture-negative paediatric patients compared against a clinical TB reference standard was very low at 4% for specimens of expectorated or induced sputum (8 studies) and 15% for samples from gastric lavage or aspiration (3 studies); the credible intervals were wide, indicating a substantial potential for over-diagnosis of TB in children using clinical TB as the reference standard. The sensitivity of Xpert MTB/RIF in detecting rifampicin resistance in specimens from children was 86% (95%CrI, 53-98%).

~~SAM~~

BAMBINI

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Use of Xpert® for the Diagnosis of Pulmonary Tuberculosis in Severely Malnourished Hospitalized Malawian Children

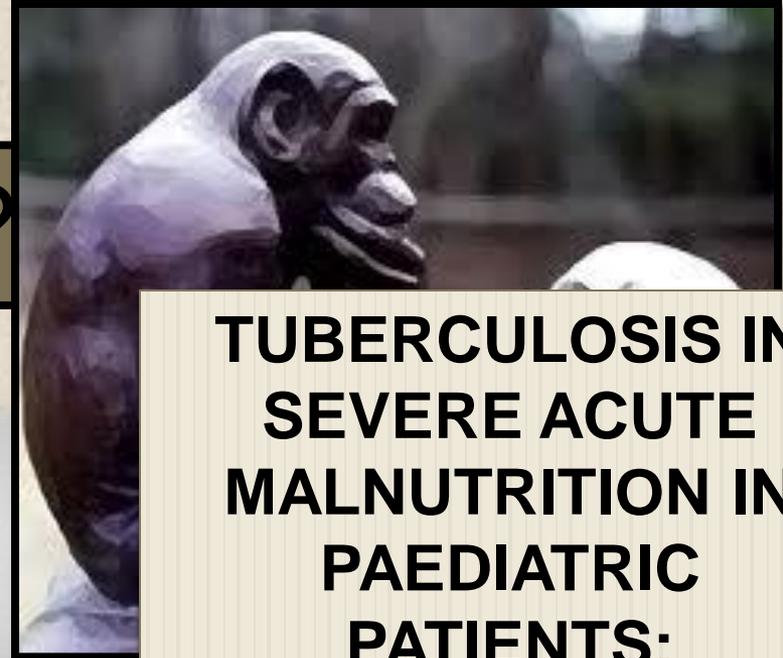
Results—Three hundred severely malnourished children (median age 18.5 months, IQR 12.1-25.6) had one induced sputum performed; 295 (98.3%) received two. Fifty-two (17.6%) were HIV-infected. Over 25% had tuberculosis exposure with 48/297 (16.2%) reporting contact and 40/287 (13.9%) with positive TST. Two (0.7%) patients had confirmed tuberculosis by Xpert and culture, but only one had positive smear microscopy. Twenty (6.7%) patients fulfilled probable and 97 (66%) met possible tuberculosis NIH case definitions. Overall mortality was 9.7%.

Conclusions—Microbiologic confirmation likely underestimates the prevalence of pulmonary tuberculosis in severely malnourished children. In our study, Xpert on induced sputums did not increase case finding. Future studies are needed using Xpert among targeted groups of severely malnourished children and on non-sputum specimens.

Twenty (6.7%) patients met NIH definitions for probable, 197 (65.7%) possible and 81 (27%) unlikely tuberculosis.

**Ma...
quindi???**

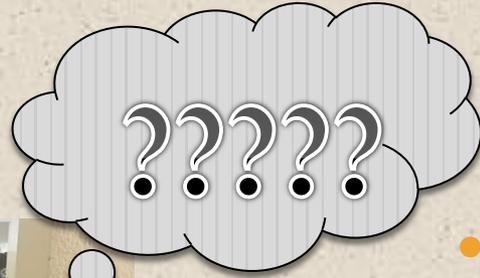
TB OR NOT TB?



**TUBERCULOSIS IN
SEVERE ACUTE
MALNUTRITION IN
PAEDIATRIC
PATIENTS:
UTILIZATION OF
TUBERCULOSIS
SCORE CHARTS AND
GENEXPERT**



Conclusioni



- Non è conosciuta la reale prevalenza dei bambini SAM affetti da Tubercolosi
- Non è previsto per i bambini SAM un percorso diagnostico diverso dai bambini normonutriti?
- Applicando il TB score si rischia di sovrastimare la tubercolosi nei bimbi con SAM?
- Il Genexpert è affidabile nei bambini con SAM?



**ASANTE SANA!
GRAZIE PER
L'ATTENZIONE!**