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A review on the evolution of the defining criteria for possible serious bacterial infection in the young infant from IMCI to IMNCI. Why the change?

Received: 18th July 2023

Accepted: 13th September 2023

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Abstract: *Introduction:* IMCI (Integrated Management of Childhood Illness) was initiated in 1997 by World Health Organization (WHO) and the United Nations International Children's Fund (UNICEF) to reduce child mortality and promote child health and development. It later evolved to Integrated Management of Childhood and Newborn Illness (IMNCI). The objective of this review is to inform, discuss and highlight the reasons which led to these improved strategies.

Method: A comprehensive literature review was conducted using electronic data bases, including Google scholar and PubMed, in which guidelines, related updates; and related studies were searched and reviewed from 1995 to 2023.

Discussion: Initially, IMCI guidelines included young infants from 1 week of age to two months, and from two months to five years. As there has been an appreciable decline in under five mortality rates, but the neonatal mortality rate is still high especially in the first week of life; new strategies were introduced particularly in the first week of life to make IMNCI. Initially, sixteen signs were used when classifying a young infant with possible serious bacterial infection (PSBI). With evidence, a reduced algorithm to seven signs was then used in young infants. Update in management of classified infection where referral is not possible in 2015 have been a big step up in reducing child mortality. Ongoing studies will provide more insight on new criteria and treatment regimens.

Conclusion: With this evolution, IMNCI has continued to be useful

in clinical practice.

Keywords: IMCI (Integrated Management of Childhood Illness), IMNCI (Integrated Management of Newborn and Childhood Illness), PSBI (Possible Serious Bacterial Infection)

Résumé: *Introduction:* La PCIME (Prise en charge intégrée des maladies de l'enfance) a été lancée en 1997 par l'Organisation mondiale de la santé (OMS) et le Fonds international des Nations Unies pour l'enfance (UNICEF) pour réduire la mortalité infantile et promouvoir la santé et le développement des enfants. Il a ensuite évolué vers la prise en charge intégrée des maladies du nouveau-né et de l'enfance (PCIMNE). L'objectif de cette revue est d'informer, de discuter et de mettre en évidence les raisons qui ont conduit à ces stratégies améliorées.

Méthodologie: Une revue complète de la littérature a été réalisée à l'aide de bases de données électroniques, notamment Google Scholar et PubMed, dans lesquelles les lignes directrices, les mises à jour associées ; et les études connexes ont été recherchées et examinées de 1995 à 2023.

Discussion: Initialement, les lignes directrices de la PCIME incluaient les jeunes nourrissons âgés de 1 semaine à deux mois et de deux mois à cinq ans. Comme il y a eu une baisse appréciable des taux de mortalité des moins de cinq ans, le taux de mortalité néonatale restant élevé, surtout au cours de la première semaine de vie, de nouvelles stratégies ont été introduites en particulier au cours

de la première semaine de vie pour aboutir à la PCIMNE. Initialement, seize signes ont été utilisés pour classer un jeune nourrisson présentant une possible infection bactérienne grave (PIBS). Avec des preuves, un algorithme réduit à sept signes a ensuite été utilisé chez les jeunes nourrissons. La mise à jour en 2015 de la prise en charge des infections

dans un contexte où la référence n'est pas possible a constitué un grand pas vers la réduction de la mortalité infantile. Les études en cours fourniront davantage d'informations sur les nouveaux critères et schémas thérapeutiques.

Conclusion : Avec cette évolution, la PCIMNE conserve son importance dans la pratique clinique.

Mots clés: PCIME (Prise en charge intégrée des maladies de l'enfant), PCIMNE (Prise en charge intégrée des maladies du nouveau-né et de l'enfant), PIBS (Possible infection bactérienne grave)

Introduction

IMCI (Integrated Management of Childhood Illness) strategy was jointly developed in 1997 by the World Health Organization (WHO) and the United Nations International Children's Fund (UNICEF) to reduce child mortality.¹ This was a response to an observation in the early 1990s by child health experts that, mostly sick children presented with signs and symptoms that were related to more than one condition and single treatments alone were not obtaining success in reducing mortality as expected. Therefore, IMCI was developed as a syndromic approach to address the overall health of the child.² IMCI focuses on three components, which are improving case management skills, strengthening health systems and improving community health practices.¹ It is a case management process for a first-level facility such as a clinic, health center or an outpatient department of a hospital.

IMCI was intended for countries with under-five mortality rates (U5MRs) higher than 40 per 1000 live births. Most of these belong to low and middle income countries (LMIC) and around one hundred countries have partially or fully adopted the IMCI strategy.³⁻⁵ With the substantial worldwide progress in reducing U5MRs since then, the global under-five mortality rate has dropped by 53%, from 91 deaths per 1,000 live births in 1990 to 43 in 2015⁶. Together with the decline in the level of mortality, the relative importance of the main causes of death has also been shifting over time.⁷

In a non-randomized study in Tanzania from 1997 to 2002, two districts with facility-based IMCI and two without IMCI were compared, and over two years, the mortality rate was 13% lower in IMCI than in comparison districts, with a rate difference of 3.8 fewer deaths per 1000 child-years.⁸ Another cluster randomized trial in Bangladesh randomly assigned ten first-level government health facilities to IMCI intervention and the other ten to usual services. In the last two years of this study, the mortality rate was 13.4% lower in IMCI than in comparison areas.⁹

IMNCI (Integrated Management of Newborn and Childhood Illness) is a term used when all children from zero to five years of age are included in the management. It was first used by India, who adopted IMCI strategy in 2003 but revised it to include all neonates and call the module IMNCI.¹⁰ Globally, all neonates (even those in

the first week of life) were included in the updated WHO module of 2008.¹¹

Bacterial infections, including sepsis, meningitis and pneumonia, account for 37% of neonatal deaths in LMIC.¹² Serious bacterial and viral infections are difficult to differentiate clinically in neonates and young infants. Early diagnosis is required through recognition of clinical signs. WHO recommends possible serious bacterial infections (PSBI) signs to be used to classify and manage these young infants.¹³

Method

A comprehensive literature review was conducted using electronic data base published in English. Google scholar and PubMed were searched where by WHO guidelines, country policy guidelines, related updates and related studies concerning IMCI, IMNCI and PSBI were thoroughly evaluated to be included in this review.

Discussion

Initially, when IMCI was introduced, ten million children were dying each year and majority of these deaths were caused by five preventable and treatable conditions namely: pneumonia, diarrhea, malaria, measles and malnutrition.¹⁴ IMCI described management using a 'cut-off' at two months of age. The young infants frequently have only general signs such as reduced movement or hypothermia, and can become sick and die very quickly from serious bacterial infections. Therefore, their assessment, classification and treatment were somewhat different from older infants or sick children aged two months up to five years.^{13,14}

In the first IMCI module of 1997, newborns in the first week of life were not involved as it was contemplated their sickness is often from conditions related to labor and delivery or conditions which require special management. Such conditions are asphyxia, sepsis from premature ruptured membranes or other intrauterine infection, or birth trauma. They may have respiratory distress due to immature lungs which begins very early on day one, and jaundice which also requires special management in the first week of life. For these reasons, management of a sick newborn was different from caring for a

young infant age one week up to two months. Therefore, training in management of these sick newborns was combined with training in labor and delivery in other courses like EmOC (Emergency Obstetric Care).¹⁴

In the first IMCI module of 1997, sixteen signs were used when assessing and classifying a sick young infant. The young infant with any of these signs; convulsions, fast breathing > 60 breaths per minute, severe chest in drawing, nasal flaring, grunting, bulging fontanelle, pus draining from ear, umbilical redness extending to skin, fever or hypothermia, many or severe skin pustules, lethargic or unconscious and less than normal movement, were classified as PSBI which may be pneumonia, sepsis or meningitis. Inability to feed was also added as a sign of PSBI.^{1,14,15}

The first IMCI update in 2005 covered six areas including antibiotic treatment of severe and non-severe pneumonia for children 2 months up to 5 years and trial of rapid acting inhaled bronchodilator for children with wheeze before they are classified as having pneumonia and prescribed antibiotics. Low osmolality oral rehydration salts (ORS) and zinc for all children with diarrhea, and antibiotic treatment for bloody diarrhea. Treatment of malaria with artemisinin-based combination therapy (ACT). Treatment of acute ear infections with oral antibiotics, and topical quinolones for chronic ear infection, infant and young child feeding and treatment of helminthiasis.^{16,17}

A change in disease epidemiology was seen globally, whereby U5MR was declining faster than that of neonatal mortality and most of these deaths occurred during the first week of life.^{17,18} It was also challenging to train and maintain first-line health workers' skills for all sixteen signs which were to be assessed in IMCI. Hence, in 2008 a multicenter study involving six countries was done, infants under 2 months of age brought with illness to health facilities were recruited in two age-groups: 0-6 days and 7-59 days. 12 symptoms or signs were used to predict severe illness in the first week of life. To improve sensitivity and specificity of the diagnostic signs and symptoms, the signs with lower sensitivity and specificity were removed, remaining with seven signs. This made the diagnosis faster without compromising the safety of the infant. The reduced algorithm to seven signs was done on the basis of prevalence of each sign or symptom, whereby sensitivity (85%) and specificity (75%) were much the same.¹⁹ These seven signs also did well in 7-59-day-old infants (sensitivity 74%, specificity 79%).²⁰

The above multicenter study, recommended a single simple algorithm to be used for identifying severe illness in infants aged 0-2 months who are brought to health facilities.²⁰ Therefore, the IMCI module updates of 2008 placed emphasis to cover mainly the sick young infant in the first two months of life, and new sections on the management of illness in the first week of a child's life were added. The young infant who was not feeding well, had convulsions, fast breathing, severe chest in drawing,

fever, low body temperature, or no/ or movement only when stimulated was classified as very severe disease. The one with either red umbilicus or draining pus or skin pustules was still classified as local bacterial infection. The one without any of the above was classified as severe disease or local infection unlikely.¹¹

This updated IMCI module of 2008 is part of the evolution of IMCI to IMNCI (Integrated Management of Newborn and Childhood Illness) whereby all neonates (including first week of life) were included in the WHO module for the first time.¹¹ Training modules were updated only in IMCI Computerized Adaptation and Training Tool (ICATT).¹¹ At that time most countries still used the term IMCI even after adaptation of the updates of 2008. The term IMNCI was initially used in India since they adopted IMCI strategy in 2003, but revised it to include all neonates and renamed it as IMNCI.¹⁰ IMNCI was adopted earlier in India because neonatal mortality contributed to over 64% of infant deaths and most of these deaths occurred during first week of life.¹⁰

Other updates in 2008 IMCI module included HIV section in high HIV settings.¹¹ Jaundice was added in signs for young infants whereby any jaundice if age less than 24 hours or yellow palms and soles at any age were classified as severe jaundice. Jaundice appearing after 24 hours of age or palms and soles not yellow were classified as jaundice. Implication of this is a potential early referral of severe jaundice and therefore reduction in morbidity such as kernicterus and mortality.¹¹

There were major updates of IMNCI in 2012, but the focus was on changes in assessment and management of children aged 2 months up to 5 years and focused on: checking general danger signs, cough or difficult breathing, diarrhea, fever/measles, ear problem, malnutrition, anemia and HIV infection.²¹

Evidence demonstrated only 25% of newborns with PSBI in resource-limited settings received hospital treatment in high-mortality settings because such treatment was not accessible, acceptable or affordable to families. The WHO recommendation for management of infections in neonates and young infants (0-59 days old) is referral for hospital treatment with a seven to ten day course of a combination of two injectable antibiotics – penicillin or ampicillin plus gentamicin.²⁰ Non-compliance with referral for hospitalization means that these infants received no treatment, resulting in unnecessary, potentially preventable infection-related newborn deaths. Common barriers to not accepting referral advice are distance to the hospital, availability of transport and other logistical reasons such as lack of child care, cost of travel and treatment, lack of permission from the husband or family elders, concerns around quality of care, a previous negative experience or poor attitudes of health workers at the hospital, cultural or religious beliefs and the absence of referral protocols/algorithms.²¹⁻²⁵

Since 2007 decisions were made to undertake research that could generate the evidence for identification and management of sick infants with PSBI when referral is not feasible. This resulted in randomized clinical trial

(RCT) in 2010-2013 led by WHO involving 3 million young infant populations in Africa and South Asia. African Neonatal Sepsis Trial (AFRINEST) was done in DRC (Democratic Republic of Congo), Kenya and Nigeria and Simplified Antibiotic Therapy Trial (SATT) was conducted in Bangladesh and Pakistan to find deliverable, effective treatment for newborns with signs of severe infection when referral is not possible.²⁶⁻²⁸

The above research resulted in global recommendations by WHO in 2015 for managing possible serious infection in young infants when referral is not possible. Young infant with fast breathing as the only sign of illness (7-59 days old) should be treated with oral amoxicillin for 7 days. Young infants 0-6 days' old with only fast breathing should be referred to hospital. Facilitate referral of all young infants with clinical signs of severe infection to a hospital. If referral is not feasible, outpatient treatment with twice daily oral amoxicillin for 7 days and injection gentamicin for 2 or 7 days. Critically ill young infants for whom referral is not accepted by families after best efforts should be treated with once daily injectable gentamicin plus at least twice daily injection ampicillin for 7 days.²⁹

Analysis of pooled individual patient-level data from three large trials in Africa and Asia showed that the WHO-recommended simplified antibiotic regimen B (oral amoxicillin and injection gentamicin) was superior to regimen A (injection procaine penicillin and injection gentamicin); and combined arms A and C (injection procaine penicillin and injection gentamicin, followed by oral amoxicillin) in terms of poor clinical outcome for the outpatient treatment of young infants with PSBI when inpatient treatment was not feasible.³⁰

Even though AFRINEST & SATT were implemented in a large population (3 million young infant) it was not implemented by the health system. Implementation research in 2015-2017 facilitated the translation of the global recommendations into country action as a bridge up to full-scale implementation. There were still issues with scale up of this intervention. As young infants are a high risk population, severe neonatal infection result in up to 15% mortality without treatment, and even with treatment there is at least 2% mortality. The complex intervention of treating PSBI with injectable and then follow-up with oral antibiotics that was not used by doctors in first level facilities caused auxiliary midwife nurse (AMN) in India to fear taking the risk by using this combination. There were also low treatment rates for young infants in Ethiopia using the IMNCI policy, possibly because of the slow roll-out of the new guidelines.^{31,32}

Challenges in implementation proved it to be essential to have technical back up and support in early implementation phase. Establishment of early implementation sites and Technical Support Units (TSU) was done in seven countries, three from Asia and 4 from Africa with a total of thirteen sites (Bangladesh—two sites; Democratic Republic of Congo—one site; Ethiopia—two sites; Malawi—one site; Nigeria—two sites; India—four sites; Pakistan—

one site).^{33,34} Thereafter, the global PSBI Community of Practice was launched in 2018 to provide a platform for technical exchange and wider dissemination of best practices, building capacity and creating a learning platform TSU.

WHO IMCI updates in 2019 focused on young infant up to two months of age and a chart booklet for young infants was made. It recommends if there is one or more of these seven signs refer urgently to hospital: not feeding well/not able to feed at all; convulsions; severe chest in drawing; high body temperature (38°C); low body temperature ($<35.5^{\circ}\text{C}$); movement only when stimulated or no movement at all or fast breathing (60 breaths per minute or more) in infants less than seven days old. These are classified as PSBI or very severe disease. If referral is refused or not feasible, treat in the clinic until referral is feasible.

Fast breathing (60 breaths per minute or more) in infants 7-59 days old is classified as pneumonia and treated with oral amoxicillin for seven days. Umbilicus red/drain pus or skin pustules are classified as local bacterial infection and should be given amoxicillin for five days. If there are no signs of bacterial infection or very severe disease means infection is unlikely.^{35,36}

WHO IMCI updates in 2019 for young infant recommendations^[35,36] assumed a similar mortality risk for all signs of possible serious infection. However, individual signs may have variable mortality risks, which may have implications for treatment strategies.^[37] Hence, in 2020, an analysis was conducted using the AFRINEST^[26,27] data to calculate the case fatality ratio (CFR) for young infants with individual or combined signs of PSBI, stratified by inpatient or outpatient treatment. It was concluded that mortality risk differs with different clinical signs.³⁸

From the findings, the young infants with a possible serious infection can be grouped into those with low-mortality risk signs (high body temperature, or severe chest in drawing or severe pneumonia); moderate-mortality risk signs (stopped feeding well, movement only when stimulated, low body temperature or multiple signs of clinical severe infection), or high-mortality risk signs (critical illness). New treatment strategies that consider differential mortality risks for the place of treatment and duration of inpatient hospital treatment could be developed and evaluated based on these findings.¹³

With the findings from the AFRINEST and reclassification of the PSBI signs and symptoms and the guidelines where referral is not possible, there is an ongoing extension of the research in six countries (Bangladesh, Ethiopia, India (two sites), Nigeria, Pakistan and Tanzania) on the "Optimizing place of treatment and antibiotic regimens for young infants presenting with signs of possible serious bacterial infection". If results show young infants with any single low-mortality risk PSBI sign can be effectively and safely treated on an outpatient basis, it may increase access to treatment for those with poor access to health facilities and allow the currently overloaded health facilities to focus on more critically ill infants.³⁸

A related ongoing study protocol, on “How long should young infants less than two months of age with moderate-mortality-risk signs of possible serious bacterial infection be hospitalized for?” will show if young infants with moderate-mortality risk PSBI signs can be safely and effectively treated on an outpatient basis after a

shorter hospital stay and reduce the burden on the hospitals, potentially reduce nosocomial hospital infections and increase access to treatment for families with poor access to health facilities.³⁹ Table 1 summarizes this evolution from when IMCI was introduced to the latest published updates.

Table 1: Summary of evolution from IMCI to IMNCI and PSBI defining criteria

Year	Updates
1997	<ul style="list-style-type: none"> • IMCI was developed by WHO and UNICEF to reduce child mortality using a syndromic approach, describing management of young infants from one week of age to two months and above two months to five years of age • Sixteen signs and symptoms were used to classify young infant illness
2005	<p>First IMCI update, covered six areas including:</p> <ul style="list-style-type: none"> • Antibiotics for pneumonia and inhaled bronchodilator for children with wheeze • ORS and zinc for diarrhea, and antibiotics for bloody diarrhea • Treatment of malaria with ACTs • Treatment of ear infections with topical quinolones • Infant and young child feeding • Treatment of helminthiasis
2008	<p>The updates covered mainly sick young infant:</p> <ul style="list-style-type: none"> • New sections on the management of illness in the first week of life (IMNCI) • The algorithm to classify PSBI for young infant were reduced to seven signs • Included HIV section in high HIV settings
2012	<ul style="list-style-type: none"> • The IMCI update focus was on changes in assessment and management of children aged 2 months up to 5 years
2015	<ul style="list-style-type: none"> • The recommendations by WHO in managing possible serious infection in young infants when referral is not possible
2019	<ul style="list-style-type: none"> • The IMNCI updates focused on young infant up to two months • Chart booklet for young infants was made, recommends classifying seven signs as PSBI or very severe disease, pneumonia, local bacterial infection or infection unlikely when there are no signs of very severe disease.
Ongoing Studies...	<ul style="list-style-type: none"> • PSBI can be grouped into high mortality risks, moderate and low mortality risks • New treatment strategies can consider differential mortality risks and duration of inpatient or outpatient treatment

Conclusion

Since IMCI was initiated in 1997 there have been several updates with current evidence from researches and available data. Possible sepsis defining criteria have also been changing to simplify the work of health personnel attending the patients and providing management even

when referral is not possible to meet the aim of reducing child mortality. Ongoing studies will provide more insight onto the functionality of the new criteria as well as regimens. With this evolution, IMNCI has continued to be useful in clinical practice.

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