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How long should young infants less than 2 months of age with moderate-mortality-risk signs of possible serious bacterial infection be hospitalized for?

Submission date
24/11/2020

Registration date
20/01/2021

Last Edited
11/09/2024

Recruitment status
No longer recruiting

Overall study status
Completed

Condition category
Infections and Infestations

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
The WHO Integrated Management of Childhood Illness (IMCI) algorithm classifies newborns and young infants up to 2 months old with clinically suspected sepsis as “Possible Serious Bacterial Infection (PSBI)”. WHO guidelines recommend that young infants with PSBI should be managed in a hospital with injectable antibiotics and supportive care. When referral to hospital is not feasible, the guidelines recommend further classification of these young infants into those who are critically ill and those who have clinical severe infection (CSI). Those with CSI, if referral is not feasible, can be managed on an outpatient basis with injectable gentamicin for 2 or 7 days and oral amoxicillin for 7 days. Implementation research on the above guidelines has demonstrated that outpatient treatment is safe and effective when hospitalization is not feasible. Overall a quarter to half of newborns in different settings are taken to a hospital. However, hospitalization has inherent risks, particularly that of nosocomial (hospital-acquired) infection with multi-drug resistant pathogens. Therefore, only those young infants with signs of PSBI who have a favourable benefit-risk ratio should be hospitalized. Studies have shown that infants with any sign of CSI had a higher mortality rate when they were hospitalized compared to when they received outpatient treatment. In contrast, the mortality rate was lower among those with any sign of critical illness who received inpatient treatment, compared to those who received outpatient treatment. This seems logical because critically ill young infants need supportive care in addition to antibiotics, whereas infants with CSI primarily need antibiotic treatment. The aim of this study is to find out whether the majority of infants with CSI who need hospitalization could be discharged early.

Who can participate?
Young infants under 2 months of age admitted to the study hospitals with moderate mortality risk signs of CSI

What does the study involve?
Infants will be discharged 48 hours after hospitalization for injectable antibiotic (gentamicin

once daily and ampicillin four times a day) and other supportive treattment, when they will be randomly allocated to either go home on oral amoxicillin for 5 more days (intervention) or continue inpatient hospital injectable antibiotic treatment and supportive therapy for a total of 7 days (control). Outcomes will be assessed on day 8 and 15 after the initiation of treatment.

What are the possible benefits and risks of participating?
The infant will receive treatment in hospital or as an outpatient. There may not be a direct benefit for the infant and society at this stage, but participation will bring benefit for future generations. If the finding of this study shows benefits for outpatient treatment, participants will have contributed to change the global recommendation on care for young infants with moderate signs of infection. If the finding of this study shows benefits for standard hospital treatment, it will be recommended for all other young infants presenting with moderate signs of infection.
It has been observed that the outpatient treatment for infants who do not have any signs of infection and have a negative laboratory test for infection after 2 days of hospital treatment for infection is associated with very low risk of mortality. However, in rare cases, the infant's condition may deteriorate despite treatment. In such rare eventuality, parents are encouraged to bring the infant back to the hospital immediately for prompt treatment and support. Additionally, parents are counselled on any danger signs that can appear in an infant while on treatment, so that they may recognize these in time and seek prompt care. The medicines being used in this study are used in infants throughout the world and are generally known to be safe, but they can rarely cause diarrhea, stomach ache or a skin rash. There is a very low risk of a serious allergic reaction, hearing problems or kidney damage. If the infant has a skin rash, diarrhea, or any other problem, the parents can always bring the infant back to the hospital for prompt treatment and support.

Where is the study run from?
World Health Organization (Switzerland)

When is the study starting and how long is it expected to run for?
January 2020 to December 2024

Who is funding the study?
Bill and Melinda Gates Foundation (USA)

Who is the main contact?
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Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
U1111-1251-1576

Study information

Scientific Title
Optimizing duration of hospitalization for young infants presenting with any moderate-mortality-risk sign of possible serious bacterial infection

Study objectives
The main hypothesis is that the poor clinical outcome in young infants with any moderate-mortality risk sign or two or more signs of CSI who clinically improve 48 hours after initiation of treatment and have a negative C-reactive protein test, who are discharged and received oral amoxicillin for next 5 days will be non-inferior to the outcome of those who will continue inpatient hospital injectable antibiotic treatment for the next 5 days.

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approved 12/06/2020, WHO Research Ethics Review Committee (20 Avenue Appia, CH-1211 Geneva 27, Switzerland; +41 (0)227912111; ercsec@who.int), ref: ERC.0003289

Study design
Multi-country interventional randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Treatment of moderate-mortality-risk signs of possible serious bacterial infection in young infants <2 months old

Interventions
Young infants <2 months of age with moderate mortality risk signs of possible serious bacterial infection (low body temperature [<35.5°C], not feeding well/stopped feeding well, movement only when stimulated or two or more low mortality risk signs) will be discharged 48 hours after hospitalization for injectable antibiotic (gentamicin injection once daily and ampicillin injection four times a day) and other supportive therapy, when they will be randomized to go home on oral amoxicillin for 5 more days (intervention) or continue inpatient hospital injectable antibiotic treatment and supportive therapy for a total of 7 days (control).

Dose of amoxicillin: (dispersible tablet 250 mg), 1/2 tablet for 1.5 to 3.9 kg body weight, and 1 tablet for 4.0 to 5.9 kg body weight, twice daily.
Duration of amoxicillin: 5 days
Mode of administration of amoxicillin: oral

Outcome assessment will be carried out by an IOA. An IOA will visit all enrolled young infants in the control arm at the hospital or at home after discharge and intervention arm enrolees at home on Day 8 and 15 of initiation of treatment.

Intervention Type
Mixed

Primary outcome measure
Poor clinical outcome defined as:
1. Death between randomization (day 3 of initiation of therapy) and day 15 of initiation of therapy, or

2. Presence of any sign of critical illness (no movement at all, unable to feed at all, or convulsions) or any sign suggestive of another serious infection, e.g. meningitis, bone or joint infection, on day 4 or day 8 of initiation of therapy, or
3. Presence of any sign of clinical severe infection (severe chest indrawing, high body temperature (>38°C), low body temperature [<35.5°C], not feeding well/stopped feeding well, movement only when stimulated, fast breathing [respiratory rate >60 breaths/minute in <7 days old]) or two or more of clinical severe infection signs on day 8 of initiation of therapy.

Secondary outcome measures
There are no secondary outcome measures

Overall study start date
01/01/2020

Completion date
31/12/2024

Eligibility

Key inclusion criteria
All patients (<2 months old at admission) admitted to the study hospitals with any moderate-mortality risk signs of clinical severe infection (CSI) at presentation (not feeding well, movement only on stimulation, low body temperature <35.5°C, two or more of the six signs of CSI) will be assessed for eligibility for this study 48 hours after initiation of treatment and considered for inclusion in the study if:
1. Clinically well on day 3 defined as the absence of all signs of critical illness (not feeding at all, no movement at all, convulsions) or CSI (not feeding well, movement only when stimulated, low body temperature (<35.5°C), high body temperature (≥38°C), severe chest indrawing, fast breathing in <7 days old)
2. C-reactive protein (CRP) test negative
3. Family lives within a catchment area where a follow-up of up to day 15 can be accomplished

Participant type(s)
Patient

Age group
Child

Upper age limit
2 Months

Sex
Both

Target number of participants
5250

Total final enrolment
5252

Key exclusion criteria
1. Weight <2 kg at the time of presentation (if age at screening is less than 10 days) or weight-for-age <-3z
2. Signs of critical illness on admission (no movement at all, unable to feed at all, or convulsions)
3. Appearance of any moderate-mortality risk sign or multiple low-mortality risk signs in the first 24 hours of life
4. Hospitalized for any illness in the previous 2 weeks
5. Prior use of injectable antibiotics for the same illness
6. Previously included in this study or currently included in any other study
7. Any other reason to stay in the hospital, as decided by the treating physician

Date of first enrolment
24/06/2021

Date of final enrolment
01/09/2024

Locations

Countries of recruitment
Bangladesh

Ethiopia

India

Nigeria

Pakistan

Tanzania

Study participating centre
Projahnmo Research Foundation (PRF)
Block A, ABANTI, House 37, Road 27
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1213

Study participating centre
Tikur Anbessa Hospital, Addis Ababa University
Addis Ababa University
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Study participating centre
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New Delhi
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Study participating centre
Community Empowerment Lab (CEL), Lucknow
26, 11, Wazir Hasan Road, Block I
Gokhale Vihar
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Study participating centre
Ahmadu Bello University Teaching Hospital, Zaria
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Study participating centre
Muhimbili University of Health and Allied Sciences
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Sponsor type
Research organisation

Website
http://www.who.int/maternal_child_adolescent/en/

ROR
https://ror.org/01f80g185

Funder(s)

Funder type
Charity

Funder Name
Bill and Melinda Gates Foundation

Alternative Name(s)
Bill & Melinda Gates Foundation, Gates Foundation, BMGF, B&MGF, GF

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United States of America

Results and Publications

Publication and dissemination plan
1. Planned publication of the protocol
2. Planned publication of the results in a high-impact peer-reviewed journal.

3. Dissemination of key findings with stakeholders will be conducted in each country after the completion of the study.

Intention to publish date
31/12/2024

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		14/07/2023	17/07/2023	Yes	No