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Can a reduced hospital stay for young infants with possible serious bacterial infection (PSBI) lead to similar or improved treatment outcomes compared to existing WHO guidelines?

Submission date
22/09/2020

Recruitment status
No longer recruiting

Registration date
09/10/2020

Overall study status
Completed

Last Edited
18/08/2024

Condition category
Infections and Infestations

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

Plain English summary of protocol

Background and study aims
Current WHO guidelines recommend that infants from birth up to 59 days of age with signs of possible serious bacterial infections (PSBI) should be managed in the hospital with injectable antibiotics and supportive care. When a referral to the hospital is not feasible or refused by the family, those with extremely severe signs (no movement at all, unable to feed at all or having convulsions) are categorized as critically ill, and those with less severe signs are classified under clinical severe infection (CSI). CSI can be managed at home on an outpatient/outreach basis with antibiotics.
The study is designed to rigorously assess treatment failure in infants in a uniform, standardized way. The ultimate goal is to evaluate the relative safety of outpatient treatment by comparing rates of treatment failure in hospital vs home care arms in low-risk infants with PSBI.

Who can participate?
Study-1: All young infants aged under 2 months old who have ONLY one of the signs of PSBI.
Study-2: All patients admitted to the study hospitals with higher risk signs of PSBI or two or more signs of CSI.

What does the study involve?
Patients in both studies will be assigned to one of 2 treatment groups i.e. hospital treatment or home treatment. Both groups will receive the same treatment and will be followed up for 15 days.

What are the possible benefits and risks of participating?
There are no additional benefits or risks. The treatment regimens prescribed for both hospital and home care infants are standard antibiotics that are part of existing WHO guidelines and whose safety has already been established.

Where is the study run from?
Community Empowerment Lab, Lucknow (India)

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

Who is funding the study?
World Health Organization (Switzerland)

Who is the main contact?
Dr Vishwajeet Kumar (scientific), vkumar@celworld.org
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
Site Protocol for Uttar Pradesh, India, Version 1.3, 3 June 2020 (Based on WHO Generic Protocol, Version 2.3 - 2 June 2020, Universal Trial Number (UTN): U1111-1251-1576, ERC0003289), CTRI /2020/11/029309

Study information

Scientific Title
Optimizing place of treatment and antibiotic regimens for young infants presenting with signs of possible serious bacterial infection

Acronym
PSBI

Study objectives
Young infants (YIs) with only one low-mortality risk sign (high body temperature ≥38°C or severe chest indrawing or fast breathing of ≥60 breaths per minute in <7 days old infants) of critical severe infection (CSI) presenting to the outpatient/emergency department of a hospital, who receive outpatient treatment, will experience a better, or at least non-inferior, clinical outcome than YIs that receive inpatient treatment. Similarly, among hospital-admitted YIs with a high-mortality risk sign (movement only when stimulated or not feeding well/stopped feeding well or low body temperature (<35.5°C)) or two or more signs of CSI who clinically improve 48 h after initiation of treatment and have a negative C-reactive protein (CRP) laboratory test (Population), does discharge from hospital on oral amoxicillin at home for the next five days (Intervention), compared with continued hospital management for next five days (Control).

Ethics approval required
Ethics approval required

Ethics approval(s)
1. approved 12/06/2020, WHO ERC (20, Avenue Appia, Geneva 27, 1211 , Switzerland; +41 22 7912111; nisary@who.int), ref: ERC.0003289

2. approved 05/07/2020, CEL IEC (26/11, Wazir Hasan Road, Lucknow , 226001 , India; +91 (0)522-4932315; irb@cel.org.in), ref: CEL/RES/202007/001

3. approved 21/07/2020, GSVM ethics committee (Room no. 125, 1st floor, GSVM Medical College, Kanpur, -, India; +91-9454581649; ecgsvm@gmail.com), ref: EC104/July/2020

4. approved 19/12/2022, SNMC Institutional Ethics Committee, India (Room no-11, 1st floor, Transfusion medicine department, SNMC, Agra, -, India; None provided; ecsnmc20@gmail.com), ref: SNMC/IEC/2022/65

Study design
Open-label two-arm individually-randomized controlled trial

Primary study design

Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Critical severe infection (CSI) or critical illness of Possible Serious Bacterial Infection (PSBI) in sick young infants

Interventions
Young infants (YIs) <2 months old visiting outpatient clinics or emergency rooms of participating hospitals will be screened for one low-mortality risk sign of CSI (study-1) or one high-mortality risk sign/multiple low-mortality risk sign of CSI (Study-2).

For study-1, YIs will be consented and randomised through a sealed envelope for outpatient /home treatment (intervention group) or inpatient/hospital treatment (control group). The outpatient treatment with injectable gentamicin (once daily) for 2 days plus oral amoxicillin (twice daily) for 7 days. The inpatient antibiotic treatment for at least 7 days initiated with WHO recommended antibiotic regimen of injectable ampicillin (four time daily) plus injectable gentamicin (once daily) along with other supportive care. Outcome assessment will be carried by visiting all enrolled young infants on day 2, 4, 8 and 15 after enrolment. Outcome assessment will be conducted at the hospital or at home after discharge in the control arm and at home in the intervention arms. Outcomes will only be ascertained by the IOAs in accordance with the outcomes criteria

For study-2, YIs who were admitted at the study hospital with relatively higher-mortality risk signs of CSI at presentation/screening will be assessed for eligibility for this study 48 h after initiation of treatment and considered for inclusion in the study if: i) clinically well on day 3 defined as absence of all signs of critical illness or CSI, and ii) Laboratory test (CRP) negative. They will be randomised using sealed envelope and assigned to intervention or control treatment group. In the intervention group, they will be discharged from hospital and treated at home with oral antibiotics for 5 days. The control group will continue inpatient hospital injectable antibiotic treatment and supportive therapy for a total of 7 days. Outcome assessment will be carried out by visiting 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.

In both the studies, all YIs will be followed up for 15 days after enrolment.

Drug dosages:
Gentamicin (strength 20 mg/ml) (Give once a day for 7 days)
Weight (kg) Dose (ml)
1.5 – 2.4 0.4
2.5 – 3.9 0.8
4.0 – 5.9 1.2

Ampicillin (strength 250 mg/1.5 ml) (Give 50 mg/kg body weight twice daily for 7 days)
Weight (kg) Dose (ml)
1.5 – 2.4 0.8
2.5 – 3.9 1.2
4.0 – 5.9 1.5

Gentamicin (I/M) (strength 20 mg/ml) (Give once a day for 2 days)
Weight (kg) Dose (ml)
1.5 – 2.4 0.4
2.5 – 3.9 0.8
4.0 – 5.9 1.2

Amoxicillin (250 mg per dose) (Give twice daily for 7 days)
Weight (kg) Dose (tablet)
1.5 – 2.4 0.5
2.5 – 3.9 0.5
4.0 – 5.9 1

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Gentamicin, amoxicillin, ampicillin

Primary outcome(s)
Measured using case report forms completed at follow up:

Study-1:
1. Death any time from randomization up to day 15 of initiation of therapy
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 2, 4 or day 8 of initiation of therapy
3. Presence of any new sign of CSI on day 4 or day 8 of initiation of therapy
4. Persistence of the presenting sign on day 8 of the initiation of therapy

Study-2:
1. Death between randomization (day 3 of initiation of therapy) and day 15 of initiation of therapy
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 8 of initiation of therapy
3. Presence of any sign of CSI on day 8 of initiation of therapy

Key secondary outcome(s))
There are no secondary outcome measures

Completion date
31/12/2024

Eligibility

Key inclusion criteria
Study-1:
1. Aged <2 months

2. Living in a geographic area where follow-up for 14 days can be accomplished presenting to outpatient clinics or emergency rooms of participating hospitals
3. ONLY one of the following low-risk signs of PSBI:
3.1. Body temperature ≥38°C
3.2. Severe chest indrawing
3.3. Fast breathing (infants aged <7 days)

Study-2:
1. Aged <2 months
2. Admitted to the study hospitals with relatively higher-mortality risk signs of 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)
3. Clinically well on day 3 defined as 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)
4. Laboratory test negative
5. Family lives within a catchment area where a follow-up of up to day 15 can be accomplished

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Neonate

Upper age limit
2 months

Sex
All

Total final enrolment
12250

Key exclusion criteria
Current exclusion criteria as of 17/10/2022:
Study-1:
1. Weight <2 kg at the time of presentation (if age at screening is less than 10 days) or weight for age <-3z
2. Appearance of low-mortality risk signs in first 24 h of life
3. Signs of critical illness (no movement at all, unable to feed at all, convulsions)
4. Signs of CSI associated with a high risk of mortality (stopped feeding well, movement only on stimulation, low body temperature < 35.5°C or two or more of the six signs of CSI)
5. Any sign suggestive of another serious illness/condition, such as major congenital malformations, severe jaundice, conditions requiring major surgery, meningitis, bone or joint infection, severe dehydration, etc.
6. Hospitalized for any illness in the previous 2 weeks
7. Prior use of injectable antibiotics for the same illness in the last 2 days excluding pre-referral

dose
8. Previously included in this study or currently included in any other study

Study-2:
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 high-mortality risk sign or multiple low-mortality risk signs in first 24 h 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 hospital, as decided by the treating physician

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Previous exclusion criteria:
Study-1:
1. Weight <2 kg at the time of presentation (if age at screening is less than 10 days) or weight for age <-3z
2. Appearance of low-mortality risk signs in first 24 h of life
3. Signs of critical illness (no movement at all, unable to feed at all, convulsions)
4. Signs of CSI associated with a high risk of mortality (stopped feeding well, movement only on stimulation, low body temperature < 35.5°C or two or more of the six signs of CSI)
5. Any sign suggestive of another serious illness/condition, such as major congenital malformations, severe jaundice, conditions requiring major surgery, meningitis, bone or joint infection, severe dehydration, etc.
6. Hospitalized for any illness in the previous 2 weeks
7. Prior use of injectable antibiotics for the same illness
8. Previously included in this study or currently included in any other study

Study-2:
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 high-mortality risk sign or multiple low-mortality risk signs in first 24 h 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 hospital, as decided by the treating physician

Date of first enrolment
07/10/2021

Date of final enrolment
10/08/2024

Locations

Countries of recruitment
India

Study participating centre
Community Empowerment Lab
A-6/14, Vineet Khand
Gomti Naga
Lucknow
India
226010

Study participating centre
Hallet District hospital
Swaroop Nagar
Kanpur
India
208002

Study participating centre
Dufferin Women's Hospital
Meston Rd
Shiwala
Patkapur
Kanpur
India
208001

Study participating centre
Shyam Children & Maternity Centre
Kalyanpur
Kanpur
India
208001

Study participating centre
Sarojani Nayadu Medical College
Moti Katra
Agra
India
282002

Sponsor information

Organisation
World Health Organization

ROR
https://ror.org/01f80g185

Funder(s)

Funder type
Research organisation

Funder Name
World Health Organization

Alternative Name(s)
, , Всемирная организация здравоохранения, Organisation mondiale de la Santé, Organización Mundial de la Salud, WHO, , BO3, OMS

Funding Body Type
Government organisation

Funding Body Subtype
International organizations

Location
Switzerland

Results and Publications

Individual participant data (IPD) sharing plan
All data generated or analysed 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?
Participant information sheet		06/04/2020	13/10/2020	No	Yes
Participant information sheet		06/04/2020	13/10/2020	No	Yes
Participant information sheet		06/04/2020	13/10/2020	No	Yes
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes

Protocol file	version v1.3	03/06/2020	13/10/2020	No	No