

A randomised trial to assess whether the addition of a beta blocker infusion (landiolol) to standard treatment in patients with septic shock, requiring prolonged (>24 hours) support with high-dose vasopressor agents, improves organ failure (the STRESS-L trial)

Submission date 04/12/2017	Recruitment status No longer recruiting	☒ Prospectively registered
		☒ Protocol
Registration date 18/12/2017	Overall study status Completed	☐ Statistical analysis plan
		☒ Results
Last Edited 29/01/2025	Condition category Infections and Infestations	☐ Individual participant data

Plain English summary of protocol

Background and study aims

Septic shock (blood poisoning) is a life-threatening condition caused by severe infection. For reasons still poorly understood, in some patients, their immune system remains excessively activated. Instead of fighting the infection, an ongoing inflammatory state results in widespread injury and failure of normal functioning of the body's vital organs, such as the lungs, heart, brain and kidneys. A hallmark of septic shock is a very low blood pressure that does not improve with an intravenous fluid drip. Despite huge research efforts over the last 20-30 years the survival rate has remained stubbornly unchanged. Outcomes have improved for sepsis in general through earlier recognition and intervention with antibiotics, however once septic shock takes hold, the risk of dying remains very high. This research project wants to see if infusing a very short-acting beta-blocker in addition to standard treatment improves organ failure in patients with septic shock. Beta-blockers are widely used to counteract the stressful long-term actions of the hormones adrenaline and noradrenaline, for example in high blood pressure, chronic heart failure, abnormally fast heart rates and cardiac rhythms, and tremor. Recently, an Italian group gave a beta-blocker to reduce, and then maintain, heart rates of patients with septic shock at between 80-95 beats per minute. They found this treatment strategy to be safe and associated with improvements in survival and reduced time in intensive care. However, their study was relatively small and recruitment occurred at a single centre so did not provide enough information to make the use of beta-blockers a mainstream recommendation. This trial aims to repeat the Rome study in approximately 35 ICUs in the UK to see if the safety and benefits that were seen can be confirmed and will also investigate the way in which beta blockers act in septic shock patients.

Who can participate?

Adults aged 18 and older who are have septic shock.

What does the study involve?

Participants are randomly allocated to one of two groups. Those in the first group receive the usual care. Those in the second group receive the usual care with the addition of landiolol. For participants in the landiolol group, the rate of the drug is adjusted until their heart rate is controlled at 80-95 beats per minute and the infusion is stopped when they are able to control their heart rate themselves. Landiolol is given intravenously (IV) as an infusion whilst a participant's heart rate is too high. This drug may be used for up to 2 weeks within the ICU where the treating team are able to monitor the participant closely. After discharge from ICU, or if the heart rate remains high after 14 days, ongoing treatment will be the decision of the treating doctor. One of the aims of this study is to better understand the biological mechanisms that are altered by beta-blockade in septic shock. As part of standard clinical care blood will be taken from a cannula (a thin tube inserted into a vein or body cavity to administer medication). Additional blood samples will be taken at study entry, on days 0, 1, 2, 4 and 6 and at the end of noradrenaline treatment (if not a sampling day). Routinely collected clinical data will be recorded for the trial. However the progress of participants will be followed at day 28 and day 90 after trial entry, at these time points the local research team will call the participant and their GP to find out how they are. The trial will not follow participants beyond 90 days.

What are the possible benefits and risks of participating?

As landiolol is an exceptionally short-acting drug, switching off the infusion is expected to reverse any possible side effects. Beta blockers are not confirmed to be useful in septic shock and it is possible that landiolol has the potential for toxicity. Full information on the possible side effects are available on request from local treating teams. The main risks are the heart could go too slowly or blood pressure could lower if a participant is sensitive to the drug. Trial participants will be closely monitored within the ICU and should they experience any side effects from the study drug, the hospital staff will take measures to stop the infusion as with any other inpatient treatment.

Where is the study run from?

This study is being run by Warwick Clinical Trials Unit (University of Warwick) and takes place in hospitals in the UK.

When is the study starting and how long is it expected to run for?

June 2017 to October 2023.

Who is funding the study?

National Institute for Health Research (UK)

Who is the main contact?

STRESS-L@warwick.ac.uk

Contact information

Type(s)

Scientific

Contact name

Dr Study Team

Contact details

Warwick Clinical Trials Unit
The University of Warwick
Gibbet Hill Road
Coventry
United Kingdom
CV4 7AL
+44 (0)2476572905
STRESS-L@warwick.ac.uk

Additional identifiers**Clinical Trials Information System (CTIS)**

2017-001785-14

Integrated Research Application System (IRAS)

213669

Central Portfolio Management System (CPMS)

35229

Study information**Scientific Title**

STudy into the REversal of Septic Shock with Landiolol (Beta Blockade)

Acronym

STRESS-L

Study objectives

A reduction in heart rate using landiolol infusion in patients with septic shock and tachycardia improves organ failure during the 14 days after the patient is started in the trial. This study is investigate whether the changes are through a reduction in cardiac and immune dysfunction.

Ethics approval required

Ethics approval required

Ethics approval(s)

Approved 09/11/2017, East of England – Essex Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, United Kingdom; +44 207 104 8107; NRESEthicsCommittee.EastofEngland-Essex@nhs.net), ref: 17/EE/0368

Primary study design

Interventional

Study design

Randomised; Interventional; Design type: Treatment, Drug

Study type(s)

Treatment

Health condition(s) or problem(s) studied

Septic shock

Interventions

Current interventions as of 28/02/2019:

Participants are randomised to receive standard treatment with the addition of a beta blocker infusion (landiolol) or standard treatment alone.

For those in the landiolol group, the rate of drug are adjusted until the heart rate is controlled between 80-94 beats per minute. Landiolol may be used for up to 14 days within the ICU. Follow up continues for up to 90 days following randomisation.

One of the aims of this study is to better understand the biological mechanisms that are altered by beta-blockade in septic shock. As part of standard clinical care blood will be taken from a cannula (a thin tube inserted into a vein or body cavity to administer medication). Additional blood samples will be taken at study entry, on days 0, 1, 2, 4 and 6 and at the end of noradrenaline treatment (if not a sampling day). These samples will be sent to University of Birmingham and University Hospitals Birmingham NHS Foundation Trust and will be used in laboratory research to help define the mechanisms involved in treating sepsis with beta blockade. These samples will be destroyed once analysis has been completed.

Routinely collected clinical data will be recorded for the trial. However the progress of participants will be followed at day 28 and day 90 after trial entry, at these time points the local research team will call the participant and their GP to find out how they are. The trial will not follow participants beyond 90 days.

Previous interventions:

Participants are randomised to receive standard treatment with the addition of a beta blocker infusion (landiolol) or standard treatment alone.

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Routinely collected clinical data will be recorded for the trial. However the progress of participants will be followed at day 28 and day 90 after trial entry, at these time points the local research team will call the participant and their GP to find out how they are. The trial will not follow participants beyond 90 days.

Intervention Type

Drug

Phase

Not Applicable

Drug/device/biological/vaccine name(s)

Landiolol

Primary outcome(s)

Organ failure is measured using the mean SOFA score over the first 14 days from entry to the trial and whilst in ICU. Measurement of the SOFA score will cease if the patient dies or is discharged from the ICU.

Key secondary outcome(s)

Current secondary outcome measures as of 12/11/2019:

1. Mortality is measured using patient records and telephone visits at day 28 and day 90
2. Length of ICU and hospital stay are measured using patient notes up to 90 days
3. Reduction in dose and duration of vasopressor treatment is measured using patient notes for up to 14 days following randomisation

Exploratory Outcome Measures:

4. Myocardial dysfunction and inflammation are measured using assays on blood samples taken on days 0, 1, 2, 4, 6 and the End of Noradrenaline Treatment Visit

Previous secondary outcome measures:

1. Mortality is measured using patient records and telephone visits at day 28 and day 90
2. Length of ICU and hospital stay are measured using patient notes up to 90 days
3. Individual organ failure-days in 28 day survivors is measured using medical tests (recording SOFA score parameters - oxygenation, renal, hepatic and coagulation function) at day 28
4. Reduction in dose and duration of vasopressor treatment (total doses of adrenaline, dobutamine, phosphodiesterase inhibitors) is measured using patient notes for up to 14 days following randomisation
5. Cardiovascular safety outcomes are measured using hospital notes for the first 14 days

Exploratory Outcome Measures:

6. Myocardial dysfunction and inflammation are measured using assays on blood samples taken on days 0, 1, 2, 4, 6 and the End of Noradrenaline Treatment Visit

Completion date

05/10/2023

Eligibility**Key inclusion criteria**

Current inclusion criteria as of 14/08/2020:

1. Aged 18 years or above
2. Being treated on an ICU
3. Septic shock according to internationally accepted definitions*
4. Heart rate ≥ 95 bpm (at the time of randomisation)
5. Receiving vasopressor support to maintain a target blood pressure for ≥ 24 hours
6. Are being treated with noradrenaline at a rate ≥ 0.1 mcg/kg/min

***Sepsis -3 definitions:**

1. Confirmed or suspected infection requiring antibiotic therapy
 2. New organ dysfunction, as evidenced by an increase in SOFA score ≥ 2
 3. A blood lactate > 2 mmol/l at any point during shock resuscitation
 4. Vasopressor therapy to maintain mean arterial pressure (MAP) ≥ 65 mmHg
- In particular the presence of a blood lactate > 2 mmol/l is only necessary for the diagnosis of septic shock and is NOT necessary for randomisation 24 hours later.

Previous inclusion criteria from 28/02/2019 to 14/08/2020:

1. Male or female aged 18 years or above
2. Being treated on an ICU
3. Septic shock according to internationally accepted definitions*
4. Heart rate ≥ 95 bpm (24 hours after start of vasopressor therapy)
5. Receiving vasopressor support to maintain a target blood pressure for ≥ 24 hours
6. Are being treated with noradrenaline at a rate ≥ 0.1 mcg/kg/min

***Sepsis -3 definitions:**

1. Confirmed or suspected infection requiring antibiotic therapy
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Previous inclusion criteria:

1. Male or female aged 18 years or above
2. Being treated on an ICU
3. Septic shock according to internationally accepted definitions*
4. Heart rate ≥ 95 bpm (24 hours after start of vasopressor therapy)
5. Receiving vasopressor support with noradrenaline to maintain a target blood pressure for ≥ 24 hours
6. Are being treated with noradrenaline at a rate ≥ 0.1 mcg/kg/min

***Sepsis -3 definitions:**

1. Confirmed or suspected infection requiring antibiotic therapy
 2. New organ dysfunction, as evidenced by an increase in SOFA score ≥ 2
 3. A blood lactate > 2 mmol/l at any point during shock resuscitation
 4. Vasopressor therapy to maintain mean arterial pressure (MAP) ≥ 65 mmHg
- In particular the presence of a blood lactate > 2 mmol/l is only necessary for the diagnosis of septic shock and is NOT necessary for randomisation 24 hours later

Participant type(s)

Patient

Healthy volunteers allowed

No

Age group

Adult

Lower age limit

18 Years

Sex

All

Key exclusion criteria

Current exclusion criteria as of 14/08/2020:

1. Tachycardia as a result of pain, discomfort from medical devices (including endotracheal tubes), during interventions or other patient distress
2. Any form of vasodilatory shock that is not caused by sepsis
3. Noradrenaline infusion $<0.1\text{mcg/kg/min}$
4. >72 hours after start of vasopressor therapy
5. <12 hours since noradrenaline to treat a medical condition after than septic shock stopped
6. Having pre-existing severe cardiac dysfunction (NYHA grade 4 or more)
7. Having pre-existing severe pulmonary hypertension (mean PA pressures $> 55\text{mmHg}$)
8. Acute severe bronchospasm (due to asthma or COPD)
9. Untreated second or third-degree heart block
10. Untreated phaeochromocytoma
11. Prinzmetal's angina
12. A past history of ischaemic stroke or transient ischaemic attack (TIA) or untreated severe carotid stenosis.
13. Advanced liver disease with Child-Pugh Score of $\geq B$.
14. Known sensitivity to beta-blockers
15. Patient/legal representative unwilling to provide written informed consent
16. Known to be pregnant
17. Terminal illness other than septic shock with a life expectancy < 28 days
18. Participants who have been administered an investigational medicinal product for another research trial in the past 30 days
19. Patients in whom the clinical team feel are about to finish their noradrenaline therapy
20. Receiving extracorporeal membrane oxygenation (ECMO) treatment

Previous exclusion criteria from 12/11/2019 to 14/08/2020:

1. Any form of compensatory tachycardia
2. Any form of vasodilatory shock that is not caused by sepsis
3. Noradrenaline infusion $<0.1\text{mcg/kg/min}$
4. >72 hours in the current cause of septic shock after start of vasopressor therapy
5. Having pre-existing severe cardiac dysfunction (NYHA grade 4 or more)
6. Having pre-existing severe pulmonary hypertension (mean PA pressures $> 55\text{mmHg}$)
7. Acute severe bronchospasm (due to asthma or COPD)
8. Untreated second or third degree heart block
9. Untreated phaeochromocytoma
10. Prinzmetal's angina
11. A past history of ischaemic stroke or transient ischaemic attack (TIA) or untreated
12. Severe carotid stenosis.
13. Advanced liver disease with Child-Pugh Score of $\geq B$.
14. Known sensitivity to beta-blockers
15. Patient/legal representative unwilling to provide written informed consent
16. Known to be pregnant
17. Terminal illness other than septic shock with a life expectancy < 28 days
18. Participants who have been administered an investigational medicinal product for
19. Another research trial in the past 30 days

20. Patients in whom the clinical team feel are about to finish their noradrenaline

21. Therapy

22. Decision of withdrawal of care is in place or imminently anticipated

Previous exclusion criteria as of 28/02/2019:

1. Noradrenaline infusion < 0.1mcg/kg/min
2. > 72 hours after start of vasopressor therapy
3. Having pre-existing severe cardiac dysfunction (NYHA grade 4 or more)
4. Having pre-existing severe pulmonary hypertension (mean PA pressures > 55mmHg)
5. Acute severe bronchospasm (due to asthma or COPD)
6. Untreated second or third degree heart block
7. Untreated phaeochromocytoma
8. Prinzmetal's angina
9. A past history of ischaemic stroke or transient ischaemic attack (TIA) or untreated severe carotid stenosis.
10. Advanced liver disease with Child-Pugh Score of $\geq$ B
11. Having been treated with any beta-blocker drug in the seventy two hours prior to screening.
12. Known sensitivity to beta-blockers
13. Patient/legal representative unwilling to provide written informed consent
14. Known to be pregnant
15. Terminal illness other than septic shock with a life expectancy < 28 days
16. Participants who have been administered an investigational medicinal product for another research trial in the past 30 days.
17. Patients in whom the clinical team feel are about to finish their noradrenaline therapy

Previous exclusion criteria:

1. Noradrenaline infusion < 0.1mcg/kg/min
2. > 48 hours after start of vasopressor therapy
3. Having pre-existing severe cardiac dysfunction (NYHA grade 4 or more)
4. Having pre-existing severe pulmonary hypertension (mean PA pressures > 55mmHg)
5. Acute severe bronchospasm (due to asthma or COPD)
6. Untreated second or third degree heart block
7. Untreated pheochromocytoma
8. Prinzmetal's angina
9. A past history of ischaemic stroke or transient ischaemic attack (TIA) or untreated severe carotid stenosis.
10. Advanced liver disease
11. Having been treated with any beta-blocker drug in the seventy two hours prior to screening.
12. Known sensitivity to beta-blockers
13. Patient/legal representative unwilling to provide written informed consent
14. Known to be pregnant
15. Terminal illness other than septic shock with a life expectancy < 28 days
16. Participants who have participated in another research trial involving an investigational medicinal product in the past 30 days.
17. Patients in whom the clinical team feel are about to finish their noradrenaline therapy

Date of first enrolment

10/01/2018

Date of final enrolment

25/09/2021

Locations

Countries of recruitment

United Kingdom

England

Northern Ireland

Scotland

Study participating centre

Queen Elizabeth Hospital

University Hospitals Birmingham NHS Foundation Trust
Trust HQ, PO Box 9551
Birmingham
United Kingdom
B15 2TH

Study participating centre

University College London Hospital

University College London Hospitals NHS Foundation Trust
250 Euston Road
London
United Kingdom
NW1 2PG

Study participating centre

Heartlands Hospital

UHB NHS Foundation Trust
Bordesley Green East
Birmingham
United Kingdom
B9 5SS

Study participating centre

Royal Victoria Hospital

Belfast Health & Social Care Trust
Grosvenor Road
Belfast
United Kingdom
BT12 6BA

Study participating centre

St. Mary's Hospital

Imperial College Healthcare NHS Trust
Praed Street
London
United Kingdom
W2 1NY

Study participating centre

Charing Cross Hospital

Imperial College Healthcare NHS Trust
Fulham Palace Rd
Hammersmith
London
United Kingdom
W6 8RF

Study participating centre

Hammersmith Hospital

Imperial College Healthcare NHS Trust
Du Cane Road
London
United Kingdom
W12 0HS

Study participating centre

Musgrove Park Hospital

Taunton & Somerset NHS Foundation Trust
Parkfield Drive
Taunton
United Kingdom
TA1 5DA

Study participating centre

King's Mill Hospital

Sherwood Forest Hospitals NHS Foundation Trust
Mansfield Road
Sutton in Ashfield
United Kingdom
NG17 4JL

Study participating centre

Bristol Royal Infirmary

University Hospitals Bristol NHS Foundation Trust
Upper Maudlin Street
Bristol
United Kingdom
BS2 8HW

Study participating centre

Queen's Medical Centre

Nottingham University Hospitals NHS Trust
Derby Road
Nottingham
United Kingdom
NG7 2UH

Study participating centre

Dorset County Hospital

Dorset County Hospital NHS Foundation Trust
Williams Ave
Dorchester
United Kingdom
DT1 2JY

Study participating centre

Royal Cornwall Hospital

Royal Cornwall Hospitals NHS Trust
Treliske
Truro
United Kingdom
TR1 3LJ

Study participating centre

Poole Hospital

Poole Hospital NHS Foundation Trust
Longfleet Road
Poole
United Kingdom
BH15 2JB

Study participating centre

Derriford Hospital

Derriford Road
Crownhill
Plymouth
United Kingdom
PL6 8DH

Study participating centre

Queen Alexandra Hospital

Portsmouth Hospitals NHS Trust
Cosham
Portsmouth
United Kingdom
PO6 3LY

Study participating centre

St Thomas' Hospital

Guy's and St Thomas' NHS Foundation Trust
Westminster Bridge Rd
Lambeth
London
United Kingdom
SE1 7EH

Study participating centre

Sunderland Royal Hospital

South Tyneside and Sunderland NHS Foundation Trust
Kayll Rd
Sunderland
United Kingdom
SR4 7TP

Study participating centre

Royal Devon & Exeter Hospital

Royal Devon & Exeter NHS Foundation Trust
Barrack Rd
Exeter
United Kingdom
EX2 5DW

Study participating centre

King's College Hospital

King's College Hospital NHS Foundation Trust
Denmark Hill
Brixton
London
United Kingdom
SE5 9RS

Study participating centre

Royal Free Hospital

Royal Free London NHS Foundation Trust
Pond St
Hampstead
London
United Kingdom
NW3 2QG

Study participating centre

Royal Liverpool Hospital

Royal Liverpool and Broadgreen University Hospitals NHS Trust
Prescot St
Liverpool
United Kingdom
L7 8XP

Study participating centre

Craigavon Area Hospital

Southern Health and Social Care Trust
68 Lurgan Rd
Portadown
Craigavon
United Kingdom
BT63 5QQ

Study participating centre

Leeds General Infirmary

Leeds Teaching Hospitals NHS Trust
Great George St
Leeds
United Kingdom
LS1 3EX

Study participating centre

Russells Hall Hospital

The Dudley Group NHS Foundation Trust
Russells Hall
Pensnett Rd
Dudley
United Kingdom
DY1 2HQ

Study participating centre

University Hospitals Coventry and Warwickshire

University Hospitals Coventry and Warwickshire NHS Trust
Clifford Bridge Rd
Coventry
United Kingdom
CV2 2DX

Study participating centre

Warwick Hospital

South Warwickshire NHS Foundation Trust
Lakin Rd
Warwick
United Kingdom
CV34 5BW

Study participating centre

Rotherham General Hospital

The Rotherham NHS Foundation Trust
Moorgate Rd
Rotherham
United Kingdom
S60 2UD

Study participating centre

York Teaching Hospital

York Teaching Hospital NHS Foundation Trust
Freeman Rd
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre

Stoke Mandeville Hospital

Buckinghamshire Healthcare NHS Trust
Mandeville Rd
Aylesbury
United Kingdom
HP21 8AL

Study participating centre

Addenbrooke's Hospital

Cambridge University Hospitals NHS Foundation Trust
Hills Rd
Cambridge
United Kingdom
CB2 0QQ

Study participating centre

Aberdeen Royal Infirmary

NHS Grampian
Foresterhill Health Campus
Aberdeen
United Kingdom
AB25 2ZN

Study participating centre

Lister Hospital

East and North Hertfordshire NHS Trust
Coreys Mill Ln
Stevenage
United Kingdom
SG1 4AB

Study participating centre

Northampton General Hospital

Northampton General Hospital NHS Trust
Northampton General Hospital
Cliftonville
Northampton
United Kingdom
NN1 5BD

Study participating centre

Hull Royal Infirmary

Hull University Teaching Hospitals NHS Trust
Anlaby Rd
Hull
United Kingdom
HU3 2JZ

Study participating centre

Royal Sussex County Hospital

Brighton and Sussex University Hospitals NHS Trust
Barry Building
Eastern Rd
Brighton
United Kingdom
BN2 5BE

Study participating centre

St George's Hospital

St George's University Hospitals NHS Foundation Trust
Cranmer Terrace
Tooting
London
United Kingdom
SW17 0RE

Study participating centre

Queen Elizabeth University Hospital Glasgow

NHS Greater Glasgow and Clyde
1345 Govan Rd
Glasgow
United Kingdom
G51 4TF

Study participating centre

Royal Victoria Infirmary

The Newcastle upon Tyne Hospitals NHS Foundation Trust
Queen Victoria Rd
Newcastle upon Tyne
United Kingdom
NE1 4LP

Sponsor information

Organisation

University Hospitals Birmingham NHS Foundation Trust

ROR

<https://ror.org/014ja3n03>

Funder(s)

Funder type

Government

Funder Name

National Institute for Health Research

Alternative Name(s)

National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type

Government organisation

Funding Body Subtype

National government

Location

United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are/will be available upon request from stress-l@warwick.ac.uk

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
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Results article		25/10 /2023	26/10 /2023	Yes	No
Protocol article		16/02 /2021	12/05 /2021	Yes	No
HRA research summary			28/06 /2023	No	No
Other publications	Pre-planned sub-study of the effect of landiolol on inflammatory and metabolomic markers	22/01 /2025	29/01 /2025	Yes	No
Study website	Study website	11/11 /2025	11/11 /2025	No	Yes