Greater Manchester and Eastern Cheshire SCN

Sepsis in Pregnancy and the Puerperium Guideline

FINAL V1
December 2021

Document Control

Ownership

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Version control

	Bolton FT local guideline V3 validated 13/12/2018	
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V0.4 V0.4i	Comments reviewed and revisions made. Inclusion of RCOG guidance re awareness of other viral infections Typos in appendix 5, section 7.1 and section 20 corrected 7/12/21	25/11/21
	Ratified by GMEC SCN Maternity Steering group	**10/12/21**

Final version V1

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Review	Review Date: Responsibility of:	23/12/21 GMEC SCN
Date placed on intranet		

Contents

1. Purpose and scope of guideline

This guideline provides guidance to all staff on the early and timely recognition and management of women with sepsis in pregnancy and the puerperium. It is essential that "moderate to high" and "high risk" sepsis and septic shock are identified and managed rapidly (as outlined in this document), because failing to do so may lead to long term morbidity from multi-organ failure and an increased risk of mortality. It is based on national and international guidance and local prescribing protocols.[1] [2]

It is intended to:

- Define the approach for screening women who are at risk of sepsis or who are unwell using the Sepsis Screening Tool
- Make explicit the first hour key interventions for women who are at high risk of death from sepsis and those for women at risk of deterioration from infection
- Explain the appropriate escalation pathways for women who are at high risk or moderate-high risk of death from sepsis and for those who are not responding to initial interventions

It is intended to be used by any staff member (nursing, midwifery or medical) who are involved in the initial assessment, admission or inpatient care of any women who may have or is developing symptoms and/or signs of infection, regardless of admission/inpatient location.

It is applicable to pregnant women and those who have given birth, had a miscarriage or a termination within the last 6 weeks.

2. Identifying people with infection and possible sepsis

Not all women with infections have sepsis, but those that are pregnant or recently delivered (within 6 weeks of delivery) are at increased risk of developing sepsis. Think '*Could this be sepsis?*' if a woman presents with signs or symptoms that indicate possible infection.

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection[3]. Once infection is suspected, assess the woman for:

- Factors that increase risk of sepsis (see section 3)
- Possible source(s) of infection (see section 4)
- Any indications of clinical concern, such as new onset abnormalities of behaviour, circulation or respiration.

The symptoms and signs of sepsis may be non-specific and/or non-localised (e.g. feeling very unwell, not having a high temperature). Pay particular attention to concerns expressed by the person and their family or carers (e.g. changes from usual behaviour).

Assess those that cannot give a good history (e.g. in those who do not speak English or with communication problems) with particular care, as they are at higher risk of death.

Calculate a MOEWS for the woman if infection or sepsis is suspected.

3. Risk factors for sepsis

Any pregnant women and those who have given birth/had a miscarriage or termination within the last 6 weeks are vulnerable to sepsis. In addition, woman with the following risk factors should be considered particularly at risk for developing sepsis:

- Impaired immune systems because of illness or drugs (e.g. long term steroids)
- Diabetes (gestational or pre-existing) or other comorbidities
- Surgery/invasive procedures (e.g. caesarean section, forceps delivery, removal of retained products of conception) in the past 6 weeks
- Continued vaginal bleeding or an offensive vaginal discharge after the above interventions or delivery of the baby
- Any breach of skin integrity (for example: cuts (including episiotomy), burns, blisters or skin infections)
- Intravenous illicit drug use
- Indwelling lines or catheters
- Prolonged rupture of membranes
- Close contact with people with group a streptococcal infection (e.g. Tonsillitis, scarlet fever)

4. Sources of infection

Consider the following when looking for the source(s) of infection (this list is not exhaustive):

System	Considerations & possible diagnoses
Genitourinary	vaginal loss (bleeding/offensive discharge), PROM, chorioamnionitis/ endometritis, infected perineum (tear repair, episiotomy), UTI/pyelonephritis
Cardiorespiratory	cough/sputum production/chest pain/shortness of breath, pneumonia/influenza/tuberculosis
Ear, Nose and Throat	sore throat/tonsillitis/pharyngitis, ear ache/otitis media, sinusitis
Gastrointestinal	abdominal pain/distension/diarrhoea ± vomiting, appendicitis, gastroenteritis
Neurological	headache/neck stiffness, change in behaviour/personality, meningitis
Skin	cellulitis/wound infection, rash, vesicles line infection, breast abscess/mastitis

Take into account the following in particular:

- Otitis media and sinusitis can lead to invasive CNS infections, including meningitis, so ensure they are excluded or, if they are the cause of the infection/sepsis, managed appropriately
- Disproportionate pain requiring opioid analgesia after vaginal delivery can be a symptom of sepsis – determine whether close contacts have signs of infection
- Where pelvic sepsis is suspected, perform a rectal and vaginal (including vulval) examination looking for pain or purulent discharge
- In cases of suspected/confirmed COVID, refer to local Management of COVID in Pregnancy guidelines.
- Remember that other viral infections such as Herpes can be a cause of life threatening sepsis

5. Remote assessment

If undertaking a remote assessment (e.g. via telephone in Triage), ask about risk factors that increase the risk of sepsis (see Section 3) or indications of clinical concern such as new onset abnormalities of behaviour, circulation or respiration, when deciding whether to offer a face-to-face-assessment and how urgently to see the woman.

Ask the woman (or relative) when she last urinated and if anyone else in the household is unwell (see section 6). Not passing urine for a prolonged period of time can be a sign that the woman is very unwell.

When asking women to attend for face to face assessment ensure attends Maternity Triage (rather than A&E)

6. Assessment

In those with suspected infection:

- Determine whether they have any additional risk factors (in Section 3)
- Take a full set of observations and calculate the MOEWS
- Look for mottled or ashen appearance, cyanosis of the skin, lips or tongue, non-blanching rash of the skin, any breach of skin integrity (for example, cuts, burns or skin infections) or other rash indicating potential infection
- Ask about frequency of urination in the past 18 hours
- Ask the woman about whether any family members are unwell; pay particular interest to those that may have a Streptococcal infection (e.g. tonsillitis)

Measure oxygen saturation in community settings if equipment is available; do not do this if it will delay further assessment or treatment.

Use the Sepsis Screening Tool (Appendix 1) to determine the **woman's risk of death** from sepsis (see section 7 for how to use the tool correctly).

Communicate with the woman and/ or her family the working diagnosis as this might elicit helpful history.

7. Sepsis Screening Tool (appendix 1)

7.1 When to use the tool and how to record its use

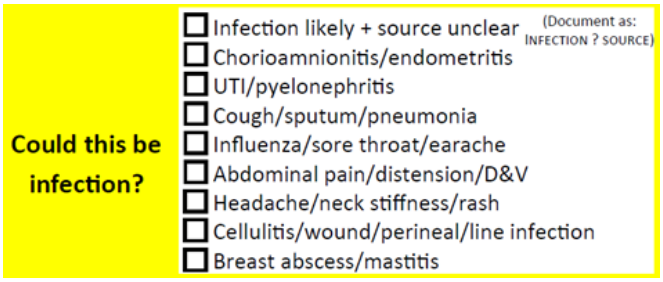
The tool should be used in any woman who is:

- Being admitted as an emergency admission (excluding women who are presenting solely for assessment of the onset of labour)
- Scoring 1 or more on the MOEWS and/or who is causing concern clinically (i.e. looks unwell even if the MOEWS is zero)

Document the time the criteria are met (or not met) in the boxes as indicated.

7.2 Using the tool – Assess for symptoms and signs of infection

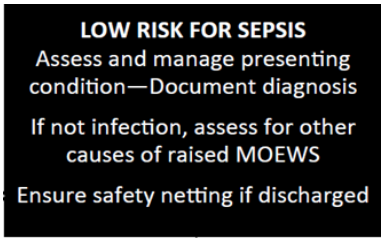
Once the woman meets one of the criteria for screening, consider whether the cause of the raised MOEWS and/or clinical concern is likely to be due to infection. The yellow box in the tool lists some of the possible causes for infection and these should be considered when assessing the woman; this list is not exhaustive.



7.3 Using the tool – infection unlikely

If infection is considered unlikely to be the cause for the raised MOEWS and/or clinical concern (e.g. elevated score is due to pre-eclampsia or post- partum haemorrhage), the woman should be escalated as per the local MOEWS algorithm and her clinical condition should be managed appropriately.

If the woman is being discharged home, provide "safety netting information" to ensure she seeks help should she deteriorate once home (see section 16).



7.4 Using the tool – Infection present and assessing for high risk criteria

If the cause of the raised MOEWS and/or clinical concern is considered to be infection, then assess the woman for any high risk criteria ("red flags"), which would indicate that she is at **high risk of death** from sepsis should they be present.

Any HIGH RISK CRITERIA? (Red flags)	☐ Responds to only voice or pain/unresponsive ☐ SBP <90mmHg (or drop >40 from normal) ☐ Heart rate >130bpm ☐ Respiratory rate ≥25 per minute ☐ Needs O_2 to keep SpO_2 ≥92% ☐ Non-blanching rash ☐ Mottled/ashen/cyanotic skin ☐ Not PU in last 18 hrs (or UO <0.5ml/kg/hr)

If the woman has **any** of these high risk criteria (red flags) commence Sepsis 6 immediately, manage as high risk for death from sepsis and continue care as defined in Section 8.

If the woman meets **any** high risk criteria (red flags) when assessed by a Midwife/Doctor in the community, arrange emergency admission to the nearest obstetric unit immediately by ambulance and alert the unit that she is on route.

7.5 Using the tool – No high risk criteria present; assessing for moderate-high risk criteria

If the woman does not have any high risk criteria, assess her for moderate to high risk criteria (in the orange box – the "orange flags"). If any of these are present, she will need further assessment and investigation, as outlined in Section 9.

Any MODERATE TO HIGH RISK criteria?	☐ Concerns about mental state ☐ RR21-24 per min/SOB ☐ HR 100-130/new arrhythmia ☐ SBP 91-100mmHg ☐ Not PU in last 12-18 hrs ☐ Temp <36°C ☐ Immunosuppressed ☐ (Gestational) diabetic ☐ Invasive procedure ☐ PROM ☐ Close contact with GAS ☐ Pathological CTG/FHR>160/sig rise in baseline ☐ Bleeding ☐Wound infection/PV discharge

If there are no high or moderate to high risk criteria but the woman's clinical status is likely to be related to infection, then she can be considered low risk of death from sepsis at this stage. She should be assessed and reviewed as directed by her symptoms and signs and given any appropriate treatments (e.g. course of oral antibiotics for an uncomplicated urinary tract infection).

8. Managing women with high risk sepsis ("red flags")

8.1 Sepsis 6

If any of the high risk criteria are present, commence the Sepsis 6 Care Bundle immediately:

	Sepsis 6 action	Rationale
1	**Ensure senior clinician attends** ST3+ or equivalent	Sepsis is a complex condition. Experience is essential to deliver the right care and confirm diagnosis.
2	**Give oxygen if required** Start if saturations <92%. Aim for saturations of 94-98%.	There is a critical imbalance between oxygen supply and demand in sepsis. Correcting low saturations helps to reduce tissue hypoxia.
3	**Obtain IV access, take bloods** Include cultures, glucose, lactate, FBC, U&Es, CRP, clotting (including fibrinogen). Consider other samples (e.g. lumbar puncture) as indicated.	Investigative tests help stratify risk and identify causative pathogens allowing more targeted antibiotic therapy.
4	**Give IV antibiotics** Maximum dose of broad spectrum therapy, according to local policy, **allergies** and need for antivirals. Give antibiotics as a bolus (rather than an infusion) where possible.	To control the source of infection, reducing the stimulus to the immune system. Increases the speed of administration and reduces dose lost in lines.
5	**Give IV fluids** Give fluid bolus of 500ml. Repeat if clinically indicated. Use lactate to guide further fluid therapy.	Hypovolaemia (absolute and relative) contributes to shock in sepsis restoring volume can help correct.
6	**Monitor** Use MOEWS. Measure urine output (may require catheter). Repeat lactate at least hourly if initial lactate elevated or clinical condition changes	Sepsis is a dynamic state. Urine output and lactate can help guide fluid therapy and determine need for ITU referral.

Ask the ST3 or above/equivalent SAS doctor to assess the woman immediately. Inform the Consultant Obstetrician and Duty Anaesthetist.

The Sepsis 6 MUST be completed within 1 hour of the high risk criteria being met. Document the time the criteria were first met in the medical records or on the Sepsis Screening Tool (when using a paper copy).

8.2 Sepsis box

The use of sepsis boxes containing the kit for initial Sepsis 6 management, is recommended to be available in admitting high risk areas and signposted clearly.

9. Managing women with moderate to high risk criteria ("orange flags")

9.1 2 or more moderate to high risk criteria met

If the woman has ≥2 moderate to high risk criteria, undertake bloods as per the Sepsis 6 table in 8.1. Ask the ST3 or above/or equivalent to review the woman's condition, with the lactate result, within an hour.

If the lactate is >2mmol/l or there is evidence of acute kidney injury (AKI, represented by a creatinine level of >135mmol/l), then treat as for high risk sepsis and initiate the Sepsis 6 Care Bundle (Section 8).

If the woman does not have a raised lactate ≥2mmol/l or AKI, monitor her at least hourly and start definitive treatment for her infection. If the diagnosis is unsure, arrange a clinical review by a senior decision maker (ST6-7 or Consultant) within 3 hours for consideration of antibiotics.

9.2 Only 1 moderate to high risk criteria met

When a woman only meets one moderate to high risk criteria:

- Ensure review by ST3 or above/or equivalent within an hour
- Perform blood tests as indicated by the woman's clinical condition, including lactate
- Treat any definitive condition
- Monitor and review hourly if the diagnosis is unclear & arrange for review by a senior decision maker (ST6-7 or Consultant) within 3 hours of meeting the criteria

10. Finding the source of infection

Take a thorough history and examine the woman carefully for sources of infection. Consider the possible sources listed in Section 4. Communicate with the woman/ her family the working diagnosis as this might elicit helpful history.

Refer to other speciality teams if appropriate (e.g. general surgeons for right iliac fossa pain suggestive of appendicitis).

10.1 Investigations

Take bloods as listed in Sepsis 6 table for those with high risk criteria or ≥2 moderate-high risk criteria. When only one moderate-high risk criteria (one “orange flag” only), send a lactate sample; other blood tests can be targeted to the woman’s clinical condition.

Undertake appropriate imaging to aid diagnosis of the source of sepsis (e.g. abdominal and pelvic ultrasound scan, chest x-ray, CT assessment).

Samples should be sent as directed by the clinical condition and may include:

- Throat swab
- Urine sample (MSSU or CSU)
- Pus swab
- Sputum sample
- Stool sample
- High vaginal swab
- Blood for serology
- Lumbar puncture (if no signs of raised intracranial pressure or contraindications; discuss this with the Anaesthetist on duty)

If the diagnosis or source of infection is unclear, consider sending all of the above samples.

All sample results must be reviewed and it is the clinical team’s responsibility to ensure that these are acted upon. The results (including negative findings) must be recorded in the woman’s medical records.

11. Antibiotics

Antibiotics should be given as per local antibiotic prescribing guidance. Ensure this is consistent with safe antibiotic use in pregnancy and breastfeeding.

The first dose of antibiotics should usually be broad spectrum (until sensitivities are known) and given as a bolus (rather than as an infusion), where not contraindicated, or as quickly as possible if bolus is prohibited.

Antibiotics must be given as soon as possible after the high risk criteria are met and must be completed within one hour.

Antiviral therapy should be commenced as early as possible in pregnant women with signs of influenza or other viral infections.

Once antibiotics are commenced, give them as per the recommended dosing schedule and avoid missing doses. If the woman does not respond to the specific therapy within 24 hours, discuss the case with the Consultant Microbiologist and consider changing to an alternative antibiotic on their advice.

Between 24 and 72 hours after initial diagnosis, review the need for and appropriateness of continued antibiotic therapy in women who are still inpatients. This decision must be documented.

If no blood cultures were sent or blood cultures are negative at 24-72 hours, the woman should be reviewed by the clinical team and the following should be documented:

- Why antibiotics need to be continued
- Rationale for antibiotic choice
- Expected duration of therapy and when to switch IV to oral

If blood cultures were sent and positive by 24-72 hours, the clinical team should:

- Document these results
- Ensure the narrowest spectrum antibiotic treatment is prescribed
- Expected duration of therapy and when to switch IV to oral

Always change to oral antibiotics as soon as possible and de-escalate to narrow spectrum therapy when sensitivities are known after discussion with the Microbiologist.

The overuse of antibiotics is linked with antibiotic resistance; ensure the protocol for their use is followed and use them judiciously in those with low risk sepsis.

12. Fluid therapy

Give intravenous balanced crystalloid such as Hartmann's solution (compound sodium lactate) in 500 millilitres boluses when the woman meets the criteria for high risk sepsis. Complete the bolus within a maximum of 15 minutes of commencing it. 0.9% sodium chloride is a suitable alternative choice.

Give a repeat bolus if there is no improvement in the woman's clinical condition after the first 500 millilitres. If there is no response to this second bolus, inform the Consultant Obstetrician and duty anaesthetist.

If the woman fails to respond to repeated fluid therapy (i.e. her BP does not improve; lactate stays raised >2mmol/l), escalate to the critical care team.

13. Monitoring and escalation to Critical Care

Increase the monitoring frequency to at least every 30 minutes, or more often/continuously if the woman is very unwell. Calculate the MOEWS each time and escalate to senior staff if it starts to deteriorate or is failing to improve.

Failure to respond is indicated by:

- Systolic BP remaining <90mmHg
- Reduced level of consciousness
- RR >25/minute or needing increasing respiratory support
- Lactate not reduced by >20% in the first hour

Inform the Consultant Obstetrician and Duty Anaesthetist if a woman with high risk criteria fails to respond within an hour of antibiotics and fluid therapy. Refer to the Critical Care team if the lactate level is >4mmol/L or if she is not responding to the antibiotics and fluids.

Consider transfer to an appropriate Critical Care area bearing in mind that she is likely to need vasopressors (e.g. noradrenaline if her BP is not responding to fluid boluses). Ensure appropriate monitoring and staff support are in place for transfer if she is moved.

In the event that a woman with a respiratory tract infection fails to respond to standard ventilatory support (after escalation to Critical Care), early advice should be sought by the Critical Care Team from a respiratory centre (e.g. for ECMO contact Saint Mary's at Wythenshawe, Manchester University NHS Foundation Trust).

14. Ongoing management

The woman should be monitored and reviewed regularly by the MDT for response to treatment. In the event that she does not respond, the Consultant Obstetrician and Consultant Anaesthetist should review the woman and further advice should be sought from the Consultant Microbiologist and/or other specialities, including Critical Care, as outlined above.

Repeat imaging is appropriate where a non-surgical, conservative approach has been used in treating collections or genital tract infection to assess the effectiveness of drug therapy. Where imaging shows conservative management has failed, surgical intervention is required to remove the source of infection.

15. Measures to reduce risk factors

All staff must adhere to local infection control protocols, both in the hospital and community settings.

16. General advice for women and their families

All pregnant women should be offered and advised about the benefits of vaccination against seasonal and pandemic flu with inactivated vaccine during the influenza season. Pregnant women should also be supported to access vaccination against Covid

Strategies for infection prevention should be discussed and the information leaflet regarding hygiene should be provided to all women (see Appendix 3).

Emphasise the following:

- The importance of frequent hand washing, particularly before and after going to the toilet, when changing sanitary towels, and after sneezing/ nose blowing
- The symptoms of sore throat and upper respiratory tract infections in both patients and close family and friends can be a risk for Group A Streptococcus infection.

17. Information for women (and their families) with suspected/ confirmed infection/sepsis

Explain the diagnosis and management plan to the woman and her family/carers and update them with new information where possible.

Women who have required inpatient treatment, particularly for high risk sepsis, should have a thorough explanation of their condition at a time when she is well again.

Offer the website links for support groups for those with sepsis (see Appendix 4).

18. Safety netting discharge information

In women determined to be at low risk of death from sepsis, provide information (see Appendix 5) about symptoms to look for and how to seek further medical help in the event of deterioration. Document the safety netting information provided.

19. Documentation

Ensure the following are clearly recorded in the woman's records:

- Time moderate to "high risk" or "moderate-high risk" criteria are met
- Time of first dose of antibiotics
- Times and management plans of clinical reviews
- Antibiotic review and rationale for the decisions made (and discussions with the Microbiologist)
- Results of relevant investigations

20. Training and education

Training in managing women presenting with sepsis will be provided for relevant staff according to individual Trust Training Needs Analysis and mandatory training schedule.

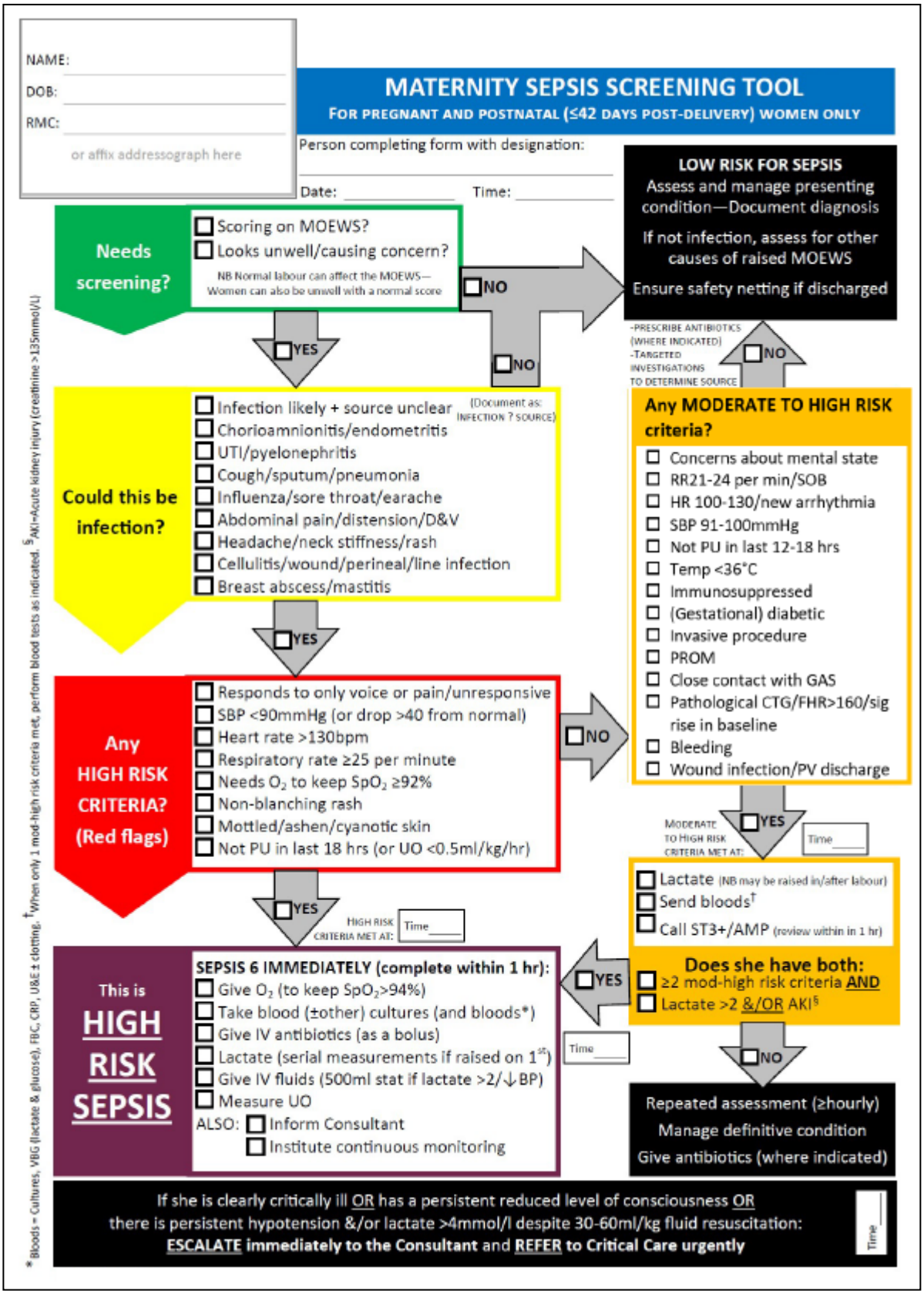
Ward Managers will run local educational drives regarding the use of the Sepsis Screening Tool, the management of sepsis and the use of antibiotics on their wards as per local needs and incident reports.

The Sepsis Screening Tool in Maternity differs from that used in other Adult areas. Any staff member who is new to Maternity (e.g. agency/bank staff, new recruits) should be supervised by a regular staff member when using the Tool initially until they are familiar with the differences (including the different trigger for screening of 1 or above on MOEWS, as opposed to 5 on the Adult National Early Warning Score).

21. Monitoring compliance

Area to be monitored	Methodology	Who	Frequency
Cases of maternal death or Adult Critical Care admission	MDT (including anaesthetics & Critical Care) case review	As per individual Trust requirements	Ad hoc
Regular audit of sepsis cases	Case note audit	As per individual Trust requirements	3 yearly

Appendix 1: Sepsis Screening Tool

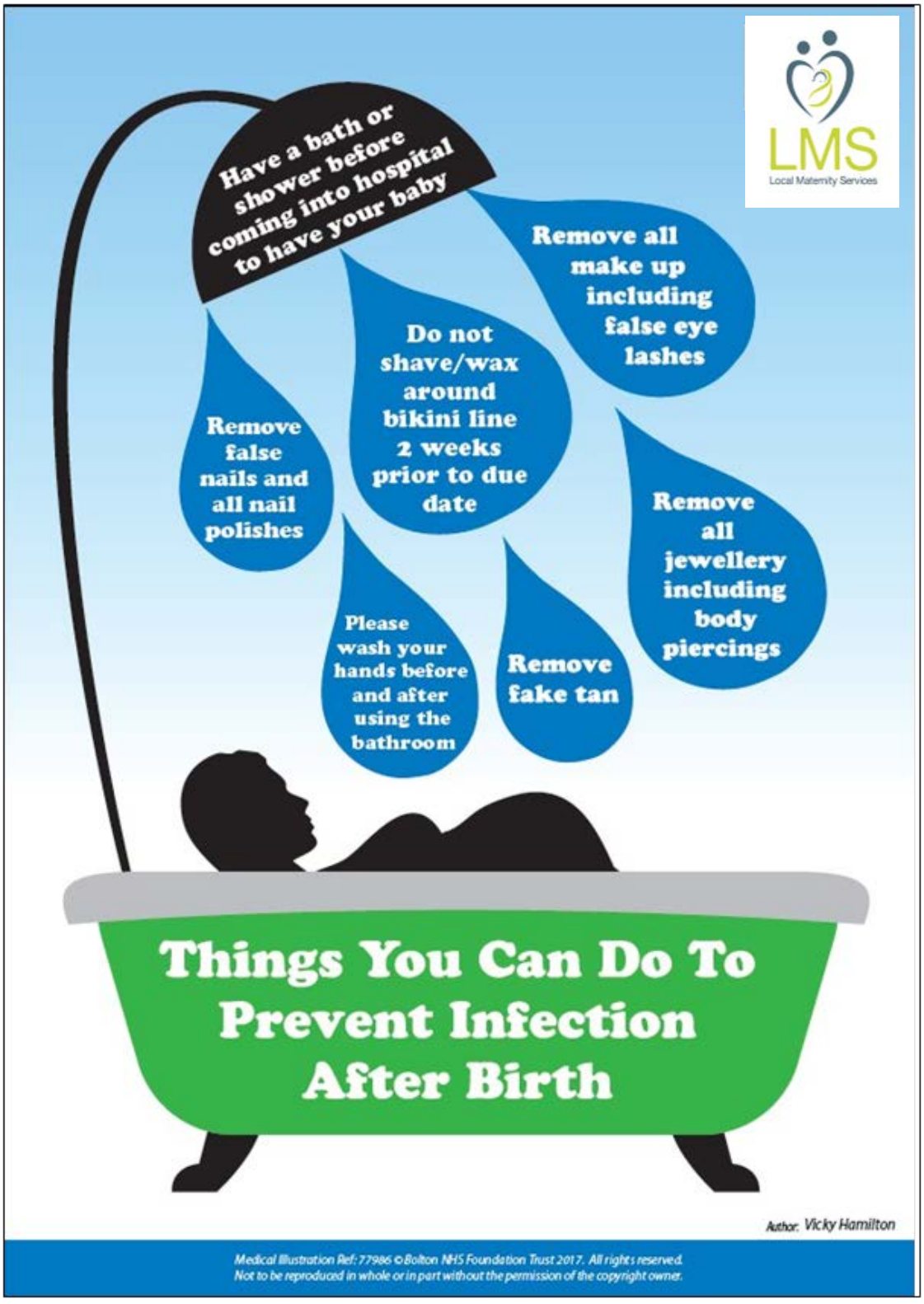


Bolton FT/SKC

Appendix 2: Modified Obstetric Early Warning Score Observation Chart

Local MOEWS chart to be inserted.

Appendix 3: Hygiene information leaflet for women and their families



Appendix 4: Patients with sepsis discharge information details

Information available about sepsis (including Safety Netting details) from: https://patient.info/health/sepsis-septicaemia-leaflet/adult-sepsis-safety-net

https://sepsistrust.org/about/about-sepsis/

Information on sepsis for women and their families: https://sepsistrust.org/get-support/resources/

https://sepsistrust.org/wp-content/uploads/2018/06/updatedNew-Booklet-27-RD.pdf

Appendix 5: Safety netting discharge information

Carbon copy sheet for completion

ADULT INFECTION DISCHARGE ADVICE

You have been assessed today in hospital and were found to have an infection. You are well enough to go home. However, you should know the signs that indicate your infection is worsening and that you may be developing *sepsis*. *Sepsis* is a reaction by the body to severe infection and is a serious condition. This leaflet helps you to recognise changes that indicate that you need to seek further medical assessment urgently.

What is Sepsis?

Sepsis (also known as blood poisoning) is the immune system's overreaction to an infection or injury. It can involve many different parts of the body.

The germs causing the infection can be bacteria, viruses or fungi.

Seek medical help URGENTLY if you develop any or one of the following

Slurred speech or confusion
Extreme shivering or muscle pain
Passing no urine (in a day)
Severe breathlessness
It feels like you're going to die
Skin mottled or discoloured

Other symptoms which could suggest sepsis include:

- VERY high temperature (fever) or low body temperature (feeling very cold)
- Feeling very sleepy or about to lose consciousness
- Severe abdominal pain
- Feeling very dizzy or faint or having a seizure (fit)
- A rash which does not fade with pressure
- Not eating any food or drink
- Vomiting (being sick) repeatedly

Call your GP immediately or ring 111 for advice

If there is any delay in talking to a doctor

CALL 999

Also seek medical advice immediately if you are concerned or your condition has changed since you last saw a doctor

For further information regarding sepsis visit www.sepsistrust.org

Who is at particular risk of sepsis?

- The elderly (over 75 years old)
- People who have had surgical procedures (or operations) or have any wounds
- People with long term lines (eg for chemotherapy) or catheters in their bladders
- Those who drink alcohol excessively
- People who inject recreational drugs
- People who have diabetes
- People with problems with their immune system
- Certain medications (eg high doses of steroids and some cancer treatments)
- Pregnant women or those who have given birth within 6 weeks (including miscarriages and terminations)

This information leaflet has been given to:	Provided by:
Name:	Name:
RMC: Fix addressograph here	Designation:
DOB:	Date: Time:

Safety netting leaflet

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SEPSIS FORUM V1.2 IPG374 review 02/22

Seek medical help URGENTLY if you develop any or one of the following:

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Extreme shivering or muscle pain
Passing no urine (in a day)
Severe breathlessness
It feels like you're going to die
Skin mottled or discoloured

SEPSIS
Every second counts

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or
Ring 111 for advice

If there is any delay in talking to a doctor
Call 999

Also, seek medical advice immediately if you are concerned or your condition has changed since you last saw a doctor

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- A rash which does not fade with pressure
- Not eating any food or drink
- Vomiting (being sick) repeatedly

Appendix 6: Equality Impact Assessment Tool

Insert local Equality Impact Assessment Tool

References

[1] NICE. Sepsis: recognition, diagnosis and early management. NICE guideline [NG 51] [Internet]. London: NICE; 2016. Available from: https://www.nice.org.uk/guidance/ng51

[2] Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2016. Crit Care Med. 2017;45(3):486-552. doi: 10.1097/CCM.0000000000002255

[3] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche J, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent J, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801–810. doi:10.1001/jama.2016.0287