

## Guidance notes:

### Natriuretic peptide (BNP) testing, oedema and sepsis.

See table on page 2 for a full listing of the concentration-dependent interpretative comments for NT-proBNP.

#### Background

Natriuretic peptides rise in conditions when there is an increase in cardiac wall stress. Different assays for measuring different peptides are available – most widely used (and recommended by NICE) is Brain-type natriuretic peptide (BNP).

N-terminal-pro-BNP (Nt-proBNP) is measured in the Trust and is freely available. BNP is the short-lived active metabolite; NT-proBNP is a long-lived stable, but inactive metabolite which is a more reliable indicator of cardiac or renal dysfunction.

The main clinical use of natriuretic peptide testing is the *exclusion* of heart failure. In a patient with breathlessness, if the NT-proBNP is low (<200 ng/L) a cardiac cause is very unlikely. NT-proBNP is a reliable (97% specific) 'rule out' test. A raised Nt-proBNP does *not* diagnose heart failure.

Note that Nt-proBNP, although very sensitive, is not *specific* for heart failure. There are many causes of a rise. It is vital to interpret the result in the clinical context. Causes of an elevated NT-proBNP include:

- A reduced left ventricular ejection fraction (systolic dysfunction) with or without heart failure
- Impaired diastolic dysfunction (stiff heart) with or without heart failure. This includes severe hypertrophy in response to hypertension or aortic stenosis
- Cardiomyopathies and amyloid heart disease
- Severe coronary disease
- Pulmonary hypertension (primary or secondary to severe respiratory disease)
  - Patients with primary respiratory disease leading to some "right heart strain" typically have an Nt-proBNP 1000 – 1500 ng/L.
- Atrial fibrillation - the great majority of patients with atrial fibrillation, in health, have an Nt-proBNP around 1000 ng/L
- Renal failure
- Age - it is particularly important to recognise that Nt-proBNP rises with age, so that the median Nt-proBNP for 80-year-olds with normal left ventricular systolic function is around 900 ng/L.
- **Sepsis/bacteraemia & COVID. See pages 2-3.**

False negative results are uncommon, but may be found in the following:

- Extreme obesity may reduce levels slightly and borderline results should be interpreted accordingly
- Constrictive pericarditis (presents with severe oedema but normal LV function on echo).

Optimal treatment for patients with heart failure is summarised in NICE guidelines:

<https://www.nice.org.uk/guidance/ng106>

The following table summarises the interpretation of NT-proBNP results.

**Note that in the acute setting, different cut-offs have been proposed. NICE suggests that an NT-proBNP below 300 ng/L excludes heart failure: in practice, an Nt-proBNP below 1000 ng/L is very unusual in a patient with acute heart failure.**

NT-proBNP concentration	Guidance/interpretation
<400 ng/L	Normal level - Heart failure unlikely in an untreated patient. If symptoms present, seek non-cardiac causes of breathlessness or oedema.
400-2000 ng/L	<b>Consider Referral to Heart Failure Service within 6 weeks</b> May be due to major structural heart disease, atrial fibrillation or major renal dysfunction (eGFR <45mL/min): modest increase in cardiovascular morbidity and mortality: if breathlessness or ankle oedema are present then these may be due to heart failure: should refer for evaluation either to the arrhythmia clinic if in atrial fibrillation, the renal clinic if gross renal dysfunction or the heart failure clinic if no cause is obvious or there is a clinical suspicion of heart failure.
2 000 – 10 000 ng/L	<b>Consider Referral to Heart Failure Service within 2 weeks</b> May be due to major structural heart disease, atrial fibrillation or major renal dysfunction (eGFR <30mL/min): moderate increase in cardiovascular morbidity and mortality: if breathlessness or ankle oedema are present then these are likely to be due to heart failure: should refer for evaluation either to the arrhythmia clinic if in atrial fibrillation, the renal clinic if gross renal dysfunction or the heart failure clinic if no cause is obvious or there is a clinical suspicion of heart failure.
>10 000 ng/L	Common in severe illness other than heart failure, particular sepsis, which should be considered. See below.

## 1.1 Sepsis/bacteraemia

Extremely high NT-proBNP levels (>10 000 ng/L) may be associated with severe illness other than heart failure, particularly sepsis. Bacteraemia is a potent stimulus to NT-proBNP release, often higher than the biochemistry assay can measure. Cancer can also cause a very high NT-proBNP. BNP release can be driven by IL-6 activation and so high levels are encountered in patients with severe COVID infection (when the IL-6 inhibitor, tocilizumab, might be used).

## 1.2 Oedema

Peripheral pitting oedema is a cardinal feature of the heart failure syndrome, but as with a raised NT-proBNP, it is *not* specific: there are many other causes of peripheral swelling. Important differentials to consider include: hypoalbuminaemia; venous insufficiency.

Patients with bacteraemia/sepsis may be confused with heart failure. Hypoalbuminaemia and “leaky” capillaries can cause peripheral oedema, and Nt-proBNP is often very high.

## 1.3 Approach to the patient with peripheral oedema

Always take a careful clinical history and examine the patient. Features suggesting heart failure include a history of ischaemic heart disease, atrial fibrillation, raised JVP (although that can be difficult to elicit with confidence) and a third heart sound. Features suggesting sepsis include high fever, vasodilation and a bounding circulation.

Before initiating treatment for heart failure, always check serum albumin and CRP. Consider measuring procalcitonin which may be minimally elevated in acute heart failure but is very high in bacteraemia. Note that fever is a feature of IL-6 production and switching off IL-6 with drugs (such as tocilizumab) may thus make infection more difficult to diagnose.

	Heart failure	Bacteraemia
Oedema	Often up to abdominal wall	Usually ankles only
Nt-proBNP	2 000 – 10 000 ng/L	Often grossly elevated (e.g. >36 000 ng/L)
Albumin	Low normal	Low
WCC	High normal	High
CRP	Modest elevation common (c. 30 mg/L)	>100 mg/L
Procalcitonin	Low level elevation possible	High
Heart rate	Usually tachycardia	Usually tachycardia
BP	Low	Low
Circulation	Cool, vasoconstricted	Warm, vasodilated

**Thanks are due to Professor Andrew L Clark, Academic Cardiology, Hull University Teaching Hospitals NHS Trust for his input into this document.**