UK Standards for Microbiology Investigations

Investigation of Bone Marrow
Acknowledgments

UK Standards for Microbiology Investigations (SMIs) are developed under the auspices of Public Health England (PHE) working in partnership with the National Health Service (NHS), Public Health Wales and with the professional organisations whose logos are displayed below and listed on the website http://www.hpa.org.uk/SMI/Partnerships. SMIs are developed, reviewed and revised by various working groups which are overseen by a steering committee (see http://www.hpa.org.uk/SMI/WorkingGroups).

The contributions of many individuals in clinical, specialist and reference laboratories who have provided information and comments during the development of this document are acknowledged. We are grateful to the Medical Editors for editing the medical content.

For further information please contact us at:
Standards Unit
Microbiology Services
Public Health England
61 Colindale Avenue
London NW9 5EQ
E-mail: standards@phe.gov.uk
Website: http://www.hpa.org.uk/SMI

UK Standards for Microbiology Investigations are produced in association with:
### Amendment Table

Each SMI method has an individual record of amendments. The current amendments are listed on this page. The amendment history is available from [standards@phe.gov.uk](mailto:standards@phe.gov.uk).

New or revised documents should be controlled within the laboratory in accordance with the local quality management system.

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<td>Status page has been renamed as Scope and Purpose and updated as appropriate.</td>
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<td>Professional body logos have been reviewed and updated.</td>
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<td>The term “CE marked leak proof container” replaces “sterile leak proof container” (where appropriate) and is referenced to specific text in the EU in vitro Diagnostic Medical Devices Directive (98/79/EC Annex 1 B 2.1) and to Directive itself EC¹,².</td>
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<td>Sections on specimen collection, transport, storage and processing.</td>
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UK SMI#: Scope and Purpose

Users of SMIs
Primarily, SMIs are intended as a general resource for practising professionals operating in the field of laboratory medicine and infection specialties in the UK. SMIs also provide clinicians with information about the available test repertoire and the standard of laboratory services they should expect for the investigation of infection in their patients, as well as providing information that aids the electronic ordering of appropriate tests. The documents also provide commissioners of healthcare services with the appropriateness and standard of microbiology investigations they should be seeking as part of the clinical and public health care package for their population.

Background to SMIs
SMIs comprise a collection of recommended algorithms and procedures covering all stages of the investigative process in microbiology from the preanalytical (clinical syndrome) stage to the analytical (laboratory testing) and postanalytical (result interpretation and reporting) stages. Syndromic algorithms are supported by more detailed documents containing advice on the investigation of specific diseases and infections. Guidance notes cover the clinical background, differential diagnosis, and appropriate investigation of particular clinical conditions. Quality guidance notes describe laboratory processes which underpin quality, for example assay validation.

Standardisation of the diagnostic process through the application of SMIs helps to assure the equivalence of investigation strategies in different laboratories across the UK and is essential for public health surveillance, research and development activities.

Equal Partnership Working
SMIs are developed in equal partnership with PHE, NHS, Royal College of Pathologists and professional societies. The list of participating societies may be found at http://www.hpa.org.uk/SMI/Partnerships. Inclusion of a logo in an SMI indicates participation of the society in equal partnership and support for the objectives and process of preparing SMIs. Nominees of professional societies are members of the Steering Committee and Working Groups which develop SMIs. The views of nominees cannot be rigorously representative of the members of their nominating organisations nor the corporate views of their organisations. Nominees act as a conduit for two way reporting and dialogue. Representative views are sought through the consultation process. SMIs are developed, reviewed and updated through a wide consultation process.

Quality Assurance
NICE has accredited the process used by the SMI Working Groups to produce SMIs. The accreditation is applicable to all guidance produced since October 2009. The process for the development of SMIs is certified to ISO 9001:2008. SMIs represent a good standard of practice to which all clinical and public health microbiology laboratories in the UK are expected to work. SMIs are NICE accredited and represent...

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6 Microbiology is used as a generic term to include the two GMC-recognised specialties of Medical Microbiology (which includes Bacteriology, Mycology and Parasitology) and Medical Virology.
neither minimum standards of practice nor the highest level of complex laboratory investigation possible. In using SMIIs, laboratories should take account of local requirements and undertake additional investigations where appropriate. SMIIs help laboratories to meet accreditation requirements by promoting high quality practices which are auditable. SMIIs also provide a reference point for method development. The performance of SMIIs depends on competent staff and appropriate quality reagents and equipment. Laboratories should ensure that all commercial and in-house tests have been validated and shown to be fit for purpose. Laboratories should participate in external quality assessment schemes and undertake relevant internal quality control procedures.

**Patient and Public Involvement**

The SMI Working Groups are committed to patient and public involvement in the development of SMIIs. By involving the public, health professionals, scientists and voluntary organisations the resulting SMI will be robust and meet the needs of the user. An opportunity is given to members of the public to contribute to consultations through our open access website.

**Information Governance and Equality**

PHE is a Caldicott compliant organisation. It seeks to take every possible precaution to prevent unauthorised disclosure of patient details and to ensure that patient-related records are kept under secure conditions. The development of SMIIs are subject to PHE Equality objectives [http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317133470313](http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317133470313).

The SMI Working Groups are committed to achieving the equality objectives by effective consultation with members of the public, partners, stakeholders and specialist interest groups.

**Legal Statement**

Whilst every care has been taken in the preparation of SMIIs, PHE and any supporting organisation, shall, to the greatest extent possible under any applicable law, exclude liability for all losses, costs, claims, damages or expenses arising out of or connected with the use of an SMI or any information contained therein. If alterations are made to an SMI, it must be made clear where and by whom such changes have been made.

The evidence base and microbial taxonomy for the SMI is as complete as possible at the time of issue. Any omissions and new material will be considered at the next review. These standards can only be superseded by revisions of the standard, legislative action, or by NICE accredited guidance.

SMIIs are Crown copyright which should be acknowledged where appropriate.

**Suggested Citation for this Document**

Scope of Document

Type of Specimen
Bone Marrow

Scope

This SMI describes the processing and microbiological investigation of bone marrow sent for clinical diagnostic purposes only.

This SMI should be used in conjunction with other SMIs.

Introduction

Microbiological examination of bone marrow is an invasive technique infrequently performed for the investigation of pyrexia of unknown origin (PUO), and occasionally for other indications. It is sometimes undertaken when other less invasive investigations and diagnostic imaging have failed to determine a cause, or, more frequently, when infection is part of the differential diagnosis in the investigation of haematological abnormalities. The demonstration of microorganisms in bone marrow, by microscopy, culture or nucleic acid amplification techniques, has been shown to be useful for diagnosis of infection with a limited number of bacteria, fungi, parasites and viruses, although some workers suggest that bone marrow cultures should not be advocated for immunocompetent patients.

Bone marrow is aspirated from the posterior iliac crest or the sternum. A core biopsy may also be collected, and this is examined histologically for evidence of granulomata and microorganisms. The aspirate is the preferred specimen for microbiological studies.

Organisms which have been Demonstrated in Bone Marrow

Some organisms invade bone marrow as part of a multi-system infection, whereas others have a tropism for bone marrow or the cell lines therein. Bone marrow cultures are useful in aiding diagnosis of a few bacterial and fungal infections. In several studies, culture of bone marrow has proved to be a faster and more sensitive method of isolating certain blood culture, particularly for Brucella and Salmonella Typhi infections. Bone marrow cultures may be positive for patients with acute, subacute and chronic brucellosis, whereas blood cultures are only positive in patients with acute infections. Cultures of bone marrow may also be positive in patients with typhoid previously treated with antibiotics.

However, it may still be difficult or impossible to culture the organism in vitro from bone marrow. One example is parvovirus B19, which infects erythroid precursors, causing a temporary cessation of red cell production. Because of its cell specificity, the virus does not grow in standard laboratory cell lines and diagnosis usually relies on serological evidence. However, viral DNA can be demonstrated in clinical specimens, including bone marrow, during both the acute illness and the chronic infection resulting from an immunosuppressed state.

Coxiella burnetii infection may occasionally cause haematological abnormalities, necessitating bone marrow examination. However, although C. burnetii has been
cultured from bone marrow, the technical difficulty and risks involved means that culture is rarely performed and the diagnosis is usually made serologically\textsuperscript{13}.

### Infections in Patients who are Immunocompromised

Conditions leading to significant immunosuppression such as advanced HIV infection, bone marrow or solid organ transplant, or high dose corticosteroid therapy predispose patients to infection with opportunistic pathogens and make disseminated infection with other pathogens more likely. In these cases culture of bone marrow may be useful in the investigation of pyrexia of unknown origin (PUO).

Organisms which may be isolated from or detected in bone marrow include the following\textsuperscript{4,5,14}:

**Bacteria**
- *Salmonella Typhi*
- *Brucella* species
- *Mycobacterium* species* (see B 40 - Investigation of Specimens for *Mycobacterium* species)

**Viruses**
- Parvovirus B19

**Fungi**
- *Histoplasma capsulatum*
- *Paracoccidioides brasiliensis*
- *Penicillium marneffei*

**Parasites**

*Leishmania* species*

*Organisms more likely to cause disseminated infection in the setting of immunosuppression*\textsuperscript{5,15}.

This is not intended to be an exhaustive list, as other organisms may be detected or isolated but includes infections where bone marrow examination is more likely to be performed.

**Organisms with Defined Geographical Endemicity\textsuperscript{4,16-19}**

**Fungi**

Infections with the dimorphic fungi *Histoplasma capsulatum* and *Paracoccidioides brasiliensis* are occasionally diagnosed on bone marrow examination\textsuperscript{20,21}.

Histoplasmosis is endemic in the USA (South-Western states), Central and South America, Senegal and sub-Saharan Africa where both *H. capsulatum* var. *capsulatum* and *H. capsulatum* var. *duboisii* coexist.

Classical *H. capsulatum* var. *capsulatum* infection is restricted to the lungs in the majority of cases and is frequently asymptomatic. However, progressive disseminated infection, often associated with underlying immunosuppression, may lead to fever,
weight loss, hepatosplenomegaly and haematological abnormalities. Involvement of any organ system, including the central nervous system, is possible.

*H. capsulatum* var. *duboisii* infection typically causes lesions in bones, skin and soft tissues, although there is also a disseminated form, which affects multiple organs including liver, spleen, kidney and lungs.

Bone marrow examination is no more sensitive than blood culture for diagnosis of infection, and the diagnosis is more frequently made by detection of the organism in respiratory specimens and other tissues. Antigen detection in serum or urine by enzyme-linked immunosorbent assay (ELISA) is also useful in progressive disseminated histoplasmosis. Complement fixation testing and double diffusion methods are also available for the detection of antibodies to *Histoplasma* and *Paracoccoides* species.

Paracoccidioidomycosis has a restricted geographical distribution in Central and South America. The chronic adult form of the disease is usually restricted to the lungs, mucosa and skin, and is thought to arise as a result of reactivation of an apparent earlier infection. The more acute and severe juvenile form frequently affects the reticuloendothelial system with predominant lymphadenopathy. It is occasionally isolated from bone marrow, although the diagnosis is usually made from examination of sputum or biopsy material.

*Penicillium marneffei* is a dimorphic soil fungus found predominantly in Southern China and South-East Asia. Disseminated infections are well described in HIV infected patients, but were very rare before the onset of the acquired immunodeficiency syndrome (AIDS) pandemic. The common clinical features include weight loss, fever, anaemia and skin lesions although cough and generalised lymphadenopathy are present in around 50%. Although fungaemia is common, occurring in 50-75% of cases, bone marrow culture is more sensitive.

**Parasites**

**Leishmania Species**

There are over 20 species of the protozoan parasite *Leishmania*. Man (an accidental host) is infected by the bite of infected female sandflies. The disease is endemic in five continents and over eighty countries. Leishmaniasis presents as three distinct syndromes, visceral (also known as Kala-azar), cutaneous and mucosal. Visceral leishmaniasis may be fatal if untreated and is characterised by fever, weight loss, hepatosplenomegaly and pancytopenia, for which bone marrow investigation is performed. Co-infection with HIV in endemic areas is associated with a more rapid progression to AIDS and infection has been transmitted through needle-sharing by infected drug users in South-West Europe. In addition to microscopy using the Giemsa stain (to detect amastigotes), culture (to detect promastigotes) and PCR should be considered for the diagnosis of *Leishmania* species (section 4). Serological diagnosis is available but it is significantly less sensitive in those with advanced HIV coinfection than for HIV negative individuals. Cross-reactions can occur in patients with prior exposure to *Trypanosoma cruzi*. Splenic puncture is the most sensitive test, but bone marrow examination is safer and has a sensitivity of around 70-80%.
Technical Information/Limitations

Limitations of UK SMIs

The recommendations made in UK SMIs are based on evidence (e.g., sensitivity and specificity) where available, expert opinion and pragmatism, with consideration also being given to available resources. Laboratories should take account of local requirements and undertake additional investigations where appropriate. Prior to use, laboratories should ensure that all commercial and in-house tests have been validated and are fit for purpose.

Selective Media in Screening Procedures

Selective media which does not support the growth of all circulating strains of organisms may be recommended based on the evidence available. A balance therefore must be sought between available evidence, and available resources required if more than one media plate is used.

Specimen Containers\(^1,2\)

SMIs use the term, “CE marked leak proof container,” to describe containers bearing the CE marking used for the collection and transport of clinical specimens. The requirements for specimen containers are given in the EU in vitro Diagnostic Medical Devices Directive (98/79/EC Annex 1 B 2.1) which states: “The design must allow easy handling and, where necessary, reduce as far as possible contamination of, and leakage from, the device during use and, in the case of specimen receptacles, the risk of contamination of the specimen. The manufacturing processes must be appropriate for these purposes.”
1 Safety Considerations

1.1 Specimen Collection, Transport and Storage

Use aseptic technique.

Ideally specimens should be collected directly into blood culture bottles, however appropriate CE marked leak proof containers and transport in sealed plastic bags may be used in some circumstances.

Compliance with postal, transport and storage regulations is essential.

1.2 Specimen Processing

Containment Level 2.

All specimens must be processed in a microbiological safety cabinet including the examination of plates and cultures.

Where Hazard Group 3 organisms, eg *Mycobacterium tuberculosis*, *Salmonella Typhi*, dimorphic fungi and *Brucella* species are suspected, all specimens must be processed in a microbiological safety cabinet under full Containment Level 3 conditions.

Laboratory procedures that give rise to infectious aerosols must be conducted in a microbiological safety cabinet.

If blood culture bottles are employed to provide an enrichment broth, then any consequent use and subsequent disposal of syringes and needles must comply with local safety protocols.

Specimen containers must also be placed in a suitable holder.

Refer to current guidance on the safe handling of all organisms documented in this SMI.

The above guidance should be supplemented with local COSHH and risk assessments.

2 Specimen Collection

2.1 Type of Specimens

Bone marrow

2.2 Optimal Time and Method of Collection

For safety considerations refer to Section 1.1.

Collect specimens before antimicrobial therapy where possible.

Specimens should ideally be collected in blood culture bottles. However, in accordance with local requirements additional specimens may be collected in appropriate CE marked leak proof containers containing anti-coagulants and placed in sealed plastic bags.
2.3 Adequate Quantity and Appropriate Number of Specimens

As large a sample as possible should be obtained, with the caveat that volumes of >3ml are likely to be contaminated with peripheral blood which may have a dilution effect.

Numbers and frequency of specimen collection are dependent on clinical condition of patient.

3 Specimen Transport and Storage

3.1 Optimal Transport and Storage Conditions

For safety considerations refer to Section 1.1.

Specimens should be transported and processed as soon as possible.

If processing is delayed, refrigeration is preferable to storage at ambient temperature.

4 Specimen Processing/Procedure

4.1 Test Selection

Select a representative portion of specimen for appropriate procedures such as culture for *Mycobacterium* species (see B 40 - Investigation of Specimens for *Mycobacterium* species).

4.2 Appearance

N/A

4.3 Sample Preparation

For safety considerations refer to Section 1.2.

4.4 Microscopy

Only carried out as indicated by local protocols, in which case a smear should be made at the patient’s bedside.

4.5 Culture and Investigation

4.5.1 Pre-treatment

If not already done, inoculate blood culture bottles with specimen and incubate and load to the automated continuous monitoring blood culture system. Subculture positive bottles as required (see B 37 - Investigation of Blood Cultures (for Organisms other than *Mycobacterium* species)).

4.5.2 Specimen processing

Standard

Bottles that flag as positive on the automated system should be subcultured according to the same procedure as for blood culture bottles (see B 37 - Investigation of Blood Cultures (for Organisms other than *Mycobacterium* species)) inoculate agar plates with
specimen from blood culture bottles (see Q 5 - Inoculation of Culture Media for Bacteriology).

### 4.5.3 Culture media, conditions and organisms

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<thead>
<tr>
<th>Clinical details/conditions</th>
<th>Standard media</th>
<th>Incubation</th>
<th>Cultures read</th>
<th>Target organism(s)</th>
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<td>Atmosphere</td>
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<tr>
<td></td>
<td>Blood agar</td>
<td>35-37</td>
<td>5–10% CO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>40-48hr</td>
</tr>
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</table>

Other organisms for consideration - Mycobacterium species (see B 40 - Investigation of Specimens for Mycobacterium species), fungi, and parasites (see B 31 - Investigation of Specimens other than Blood for Parasites) *Incubation times may be increased up to five days if Brucella infections are suspected<sup>41</sup>*

### 4.6 Identification

#### 4.6.1 Minimum level of identification in the laboratory

All organisms to species level.

**Note 1:** Any organism considered to be a contaminant may not require identification to species level.

**Note 2:** All work on suspected *Salmonella* Typhi, *Mycobacterium* species, dimorphic fungi and *Brucella* species must be performed in a microbiological safety cabinet under Containment Level 3 conditions.

Refer to individual SMIs for organism identification.

### 4.7 Antimicrobial Susceptibility Testing

Refer to British Society for Antimicrobial Chemotherapy (BSAC) and/or EUCAST guidelines.

### 4.8 Referral for Outbreak Investigations

N/A

### 4.9 Referral to Reference Laboratories

For information on the tests offered, turnaround times, transport procedure and the other requirements of the reference laboratory click here for user manuals and request forms.
Organisms with unusual or unexpected resistance, and whenever there is a laboratory or clinical problem, or anomaly that requires elucidation should, be sent to the appropriate reference laboratory.

Fungi Identification and/or susceptibility testing.

http://www.hpa.org.uk/cfi/mycology/default.htm

*Mycobacterium* Identification and susceptibility testing.

*Brucella* species Identification and/or susceptibility testing

http://www.hpa.org.uk/cfi/other_ref_labs/br.htm

Bone marrow specimens for the identification of *Leishmania* species should be sent to either:

Department of Clinical Parasitology
Hospital for Tropical Diseases
3rd Floor
Mortimer Market
Capper Street
London WC1E 6JB

http://www.thehtd.org/Parasitology.aspx

Or

Diagnostic Parasitology Laboratory
Liverpool School of Tropical Medicine
Pembroke Place
Liverpool L3 5QA

http://www.liv.ac.uk/lstm/travel_health_services/diagnos_lab.htm

Isolates associated with outbreaks, where epidemiologically indicated and organisms with unusual or unexpected resistance and whenever there is a laboratory or clinical problem or anomaly that requires elucidation should be sent to the appropriate reference laboratory.

Contact appropriate devolved national reference laboratory for information on the tests available, turnaround times, transport procedure and any other requirements for sample submission:

England and Wales
http://www.hpa.org.uk/webw/HPAweb&Page&HPAwebAutoListName/Page/1158313434370

Scotland

Northern Ireland

http://www.publichealth.hscni.net/directorate-public-health/health-protection

5 Reporting Procedure

5.1 Microscopy

Dependent upon local protocols.
5.1.1 Microscopy reporting time
Urgent microscopy results to be telephoned or sent electronically.
Written report 16–72hr.

5.2 Culture
Report clinically significant isolates or
Report other growth or
Report absence of growth.

5.2.1 Culture reporting time
Clinically urgent results to be telephoned or sent electronically.
Written report: 16–72hr stating, if appropriate, that a further report will be issued.

5.3 Antimicrobial Susceptibility Testing
Report susceptibilities as clinically indicated. Prudent use of antimicrobials according to local and national protocols is recommended.

6 Notification to PHE or Equivalent in the Devolved Administrations

The Health Protection (Notification) regulations 2010 require diagnostic laboratories to notify Public Health England (PHE) when they identify the causative agents that are listed in Schedule 2 of the Regulations. Notifications must be provided in writing, on paper or electronically, within seven days. Urgent cases should be notified orally and as soon as possible, recommended within 24 hours. These should be followed up by written notification within seven days.

For the purposes of the Notification Regulations, the recipient of laboratory notifications is the local PHE Health Protection Team. If a case has already been notified by a registered medical practitioner, the diagnostic laboratory is still required to notify the case if they identify any evidence of an infection caused by a notifiable causative agent.

Notification under the Health Protection (Notification) Regulations 2010 does not replace voluntary reporting to PHE. The vast majority of NHS laboratories voluntarily report a wide range of laboratory diagnoses of causative agents to PHE and many PHE Health Protection Teams have agreements with local laboratories for urgent reporting of some infections. This should continue.

Note: The Health Protection Legislation Guidance (2010) includes reporting of Human Immunodeficiency Virus (HIV) & Sexually Transmitted Infections (STIs), Healthcare Associated Infections (HCAIs) and Creutzfeldt–Jakob disease (CJD) under ‘Notification Duties of Registered Medical Practitioners’: it is not noted under ‘Notification Duties of Diagnostic Laboratories’.

http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/HealthProtectionRegulations/

Other arrangements exist in Scotland, Wales and Northern Ireland.
References

1. European Parliament. UK Standards for Microbiology Investigations (SMIs) use the term "CE marked leak proof container" to describe containers bearing the CE marking used for the collection and transport of clinical specimens. The requirements for specimen containers are given in the EU in vitro Diagnostic Medical Devices Directive (98/79/EC Annex 1 B 2.1) which states: "The design must allow easy handling and, where necessary, reduce as far as possible contamination of, and leakage from, the device during use and, in the case of specimen receptacles, the risk of contamination of the specimen. The manufacturing processes must be appropriate for these purposes".


