

NATIONAL STANDARD METHOD

INVESTIGATION OF BONE MARROW

BSOP 38

Issued by Standards Unit, Evaluations and Standards Laboratory
Centre for Infections



Association of Medical Microbiologists
Association of Medical Microbiologists
Association of Medical Microbiologists



INVESTIGATION OF BONE MARROW

Issue no: 1 Issue date: 09.11.07 Issued by: Standards Unit, Evaluations and Standards Laboratory
BSOP 38i1

Page no: 1 of 16

This SOP should be used in conjunction with the series of other SOPs from the Health Protection Agency

www.evaluations-standards.org.uk

Email: standards@hpa.org.uk

STATUS OF NATIONAL STANDARD METHODS

National Standard Methods, which include standard operating procedures (SOPs), algorithms and guidance notes, promote high quality practices and help to assure the comparability of diagnostic information obtained in different laboratories. This in turn facilitates standardisation of surveillance underpinned by research, development and audit and promotes public health and patient confidence in their healthcare services. The methods are well referenced and represent a good minimum standard for clinical and public health microbiology. However, in using National Standard Methods, laboratories should take account of local requirements and may need to undertake additional investigations. The methods also provide a reference point for method development.

National Standard Methods are developed, reviewed and updated through an open and wide consultation process where the views of all participants are considered and the resulting documents reflect the majority agreement of contributors.

Representatives of several professional organisations, including those whose logos appear on the front cover, are members of the working groups which develop National Standard Methods. Inclusion of an organisation's logo on the front cover implies support for the objectives and process of preparing standard methods. The representatives participate in the development of the National Standard Methods but their views are not necessarily those of the entire organisation of which they are a member. The current list of participating organisations can be obtained by emailing standards@hpa.org.uk.

The performance of standard methods depends on the quality of reagents, equipment, commercial and in-house test procedures. Laboratories should ensure that these have been validated and shown to be fit for purpose. Internal and external quality assurance procedures should also be in place.

Whereas every care has been taken in the preparation of this publication, the Health Protection Agency or any supporting organisation cannot be responsible for the accuracy of any statement or representation made or the consequences arising from the use of or alteration to any information contained in it. These procedures are intended solely as a general resource for practising professionals in the field, operating in the UK, and specialist advice should be obtained where necessary. If you make any changes to this publication, it must be made clear where changes have been made to the original document. The Health Protection Agency (HPA) should at all times be acknowledged.

The HPA is an independent organisation dedicated to protecting people's health. It brings together the expertise formerly in a number of official organisations. More information about the HPA can be found at www.hpa.org.uk.

The HPA aims to be a fully 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 conditions¹.

More details can be found on the website at www.evaluations-standards.org.uk. Contributions to the development of the documents can be made by contacting standards@hpa.org.uk.

Please note the references are now formatted using Reference Manager software. If you alter or delete text without Reference Manager installed on your computer, the references will not be updated automatically.

Suggested citation for this document:

Health Protection Agency (2007). Investigation of bone marrow. National Standard Method BSOP 38 Issue 1. http://www.hpa-standardmethods.org.uk/pdf_sops.asp.

INVESTIGATION OF BONE MARROW

Issue no: 1 Issue date: 09.11.07 Issued by: Standards Unit, Evaluations and Standards Laboratory
BSOP 38i1

Page no: 2 of 16

This SOP should be used in conjunction with the series of other SOPs from the Health Protection Agency

www.evaluations-standards.org.uk

Email: standards@hpa.org.uk

INDEX

| | |
|--|-----------|
| INVESTIGATION OF BONE MARROW | 1 |
| STATUS OF NATIONAL STANDARD METHODS | 2 |
| INDEX..... | 3 |
| AMENDMENT PROCEDURE | 4 |
| INVESTIGATION OF BONE MARROW | 5 |
| SCOPE OF DOCUMENT | 5 |
| INTRODUCTION | 5 |
| TECHNICAL INFORMATION | 7 |
| 1 SAFETY CONSIDERATIONS | 8 |
| 1.1 SPECIMEN COLLECTION | 8 |
| 1.2 SPECIMEN TRANSPORT AND STORAGE | 8 |
| 1.3 SPECIMEN PROCESSING..... | 8 |
| 2 SPECIMEN COLLECTION | 8 |
| 2.1 OPTIMAL TIME OF SPECIMEN COLLECTION | 8 |
| 2.2 CORRECT SPECIMEN TYPE AND METHOD OF COLLECTION | 8 |
| 2.3 ADEQUATE QUANTITY AND APPROPRIATE NUMBER OF SPECIMENS | 8 |
| 3 SPECIMEN TRANSPORT AND STORAGE | 8 |
| 3.1 TIME BETWEEN SPECIMEN COLLECTION AND PROCESSING..... | 8 |
| 3.2 SPECIAL CONSIDERATIONS TO MINIMISE DETERIORATION | 8 |
| 4 SPECIMEN PROCESSING | 8 |
| 4.1 TEST SELECTION | 8 |
| 4.2 APPEARANCE | 9 |
| 4.3 MICROSCOPY | 9 |
| 4.4 CULTURE AND INVESTIGATION | 9 |
| 4.5 IDENTIFICATION | 10 |
| 4.6 ANTIMICROBIAL SUSCEPTIBILITY TESTING | 11 |
| 5 REPORTING PROCEDURE..... | 11 |
| 5.1 MICROSCOPY | 11 |
| 5.2 CULTURE | 11 |
| 5.3 ANTIMICROBIAL SUSCEPTIBILITY TESTING | 11 |
| 6 REPORTING TO THE HPA (LOCAL AND REGIONAL SERVICES AND CENTRE FOR INFECTIONS)..... | 12 |
| 7 ACKNOWLEDGEMENTS AND CONTACTS..... | 13 |
| REFERENCES | 14 |

INVESTIGATION OF BONE MARROW

Issue no: 1 Issue date: 09.11.07 Issued by: Standards Unit, Evaluations and Standards Laboratory Page no: 3 of 16
BSOP 38i1

This SOP should be used in conjunction with the series of other SOPs from the Health Protection Agency

www.evaluations-standards.org.uk

Email: standards@hpa.org.uk

AMENDMENT PROCEDURE

| | |
|-------------------------------|------------------------------|
| Controlled document reference | BSOP 38 |
| Controlled document title | Investigation of bone marrow |

Each National Standard Method has an individual record of amendments. The current amendments are listed on this page. The amendment history is available from standards@hpa.org.uk.

On issue of revised or new pages each controlled document should be updated by the copyholder in the laboratory.

| Amendment Number/ Date | Issue no. Discarded | Insert Issue no. | Page | Section(s) involved | Amendment |
|---------------------------|------------------------|------------------------|------|---------------------|-----------|
| | | | | | |

INVESTIGATION OF BONE MARROW

Issue no: 1 Issue date: 09.11.07 Issued by: Standards Unit, Evaluations and Standards Laboratory Page no: 4 of 16
BSOP 38i1

This SOP should be used in conjunction with the series of other SOPs from the Health Protection Agency

www.evaluations-standards.org.uk

Email: standards@hpa.org.uk

INVESTIGATION OF BONE MARROW

Types of specimen: Bone marrow

SCOPE OF DOCUMENT

This National Standard Methods (NSM) describes the processing and microbiological investigation of bone marrow sent for clinical diagnostic purposes only.

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 cause², 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 viruses³, although some workers suggest that bone marrow cultures should not be advocated for immunocompetent patients⁴.

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 studies³.

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 isolation than blood culture⁵⁻⁸, 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 infections⁹. Cultures of bone marrow may also be positive in patients with typhoid previously treated with antibiotics¹⁰.

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 state¹¹.

Coxiella burnetii infection may occasionally cause haematological abnormalities, necessitating bone marrow examination. However, although *C. burnetii* has been cultured from bone marrow¹², the technical difficulty and risks involved means that culture is rarely performed and the diagnosis is usually made serologically.

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^{3,4,13}:

Bacteria

- *Salmonella* Typhi

INVESTIGATION OF BONE MARROW

Issue no: 1 Issue date: 09.11.07 Issued by: Standards Unit, Evaluations and Standards Laboratory
BSOP 38i1

Page no: 5 of 16

This SOP should be used in conjunction with the series of other SOPs from the Health Protection Agency

www.evaluations-standards.org.uk

Email: standards@hpa.org.uk

- *Brucella* species
- *Mycobacterium* species* (see [BSOP 40 - Investigation of specimens for Mycobacterium species](#))

Viruses

- Parvovirus B19

Fungi

- *Histoplasma capsulatum**
- *Paracoccidioides brasiliensis**
- *Penicillium marneffeii**

Parasites

- *Leishmania* species*

*Organisms more likely to cause disseminated infection in the setting of immunosuppression^{4,14-17}

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^{3,18-21}

Fungi

Infections with the dimorphic fungi *Histoplasma capsulatum* and *Paracoccidioides brasiliensis* are occasionally diagnosed on bone marrow examination^{22,23}.

Histoplasmosis is endemic in the USA (Southwestern 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 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* spp.

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 inapparent 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 marneffeii is a dimorphic soil fungus found predominantly in Southern China and SE Asia. Disseminated infections are well described in HIV infected patients but were very rare before the onset of the 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^{24,25}.

INVESTIGATION OF BONE MARROW

Issue no: 1 Issue date: 09.11.07 Issued by: Standards Unit, Evaluations and Standards Laboratory Page no: 6 of 16
BSOP 38i1

This SOP should be used in conjunction with the series of other SOPs from the Health Protection Agency

www.evaluations-standards.org.uk

Email: standards@hpa.org.uk

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 untreated¹⁸ 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 Europe¹⁹. 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 4.3.2). Serological diagnosis is available but it is significantly less sensitive in those with advanced HIV coinfection than for HIV negative individuals²⁶. Cross-reactions can occur in patients with prior exposure to *Trypanosoma cruzi*²⁰. Splenic puncture is the most sensitive test, but bone marrow examination is safer and has a sensitivity of around 70 - 80%.

TECHNICAL INFORMATION

N/A

INVESTIGATION OF BONE MARROW

Issue no: 1 Issue date: 09.11.07 Issued by: Standards Unit, Evaluations and Standards Laboratory Page no: 7 of 16
BSOP 38i1

This SOP should be used in conjunction with the series of other SOPs from the Health Protection Agency

www.evaluations-standards.org.uk

Email: standards@hpa.org.uk

1 SAFETY CONSIDERATIONS^{14-17,27-33}

1.1 SPECIMEN COLLECTION

Appropriate hazard labelling according to local policy.

Refer to relevant HSE/COSHH guidelines on the collection and safe handling of specimens likely to contain Category 3 pathogens.

1.2 SPECIMEN TRANSPORT AND STORAGE

Ideally should be collected directly into blood culture bottles however a sterile leakproof container in a sealed plastic bag may be used in some circumstances.

1.3 SPECIMEN PROCESSING

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

NOTE: 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.

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

2 SPECIMEN COLLECTION

2.1 OPTIMAL TIME OF SPECIMEN COLLECTION

Before antimicrobial therapy where possible.

2.2 CORRECT SPECIMEN TYPE AND METHOD OF COLLECTION

Specimens should ideally be collected in blood culture bottles. However, in accordance with local requirements additional specimens may be collected in sterile containers containing anti-coagulants.

2.3 ADEQUATE QUANTITY AND APPROPRIATE NUMBER OF SPECIMENS

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

3 SPECIMEN TRANSPORT AND STORAGE

3.1 TIME BETWEEN SPECIMEN COLLECTION AND PROCESSING

Specimens should be transported and processed as soon as possible.

3.2 SPECIAL CONSIDERATIONS TO MINIMISE DETERIORATION

If processing is delayed, refrigeration for up to 48 h is preferable to storage at ambient temperature. Delays of over 48 h are undesirable³⁴.

4 SPECIMEN PROCESSING

4.1 TEST SELECTION

Select a representative portion of specimen for appropriate procedures such as culture for *Mycobacterium* species (see [BSOP 40 - Investigation of specimens for Mycobacterium species](#))

INVESTIGATION OF BONE MARROW

Issue no: 1 Issue date: 09.11.07 Issued by: Standards Unit, Evaluations and Standards Laboratory Page no: 8 of 16
BSOP 38i1

This SOP should be used in conjunction with the series of other SOPs from the Health Protection Agency

www.evaluations-standards.org.uk

Email: standards@hpa.org.uk

4.2 APPEARANCE

N/A

4.3 MICROSCOPY

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

4.4 CULTURE AND INVESTIGATION

4.4.1 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 [BSOP 37 - Investigation of blood cultures \(for organisms other than Mycobacterium species\)](#))

4.4.2 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 [BSOP 37 - Investigation of blood cultures \(for organisms other than Mycobacterium species\)](#)) inoculate agar plates with specimen from blood culture bottles (see [QSOP 52 - Inoculation of culture media \(formerly BSOP 54\)](#))

INVESTIGATION OF BONE MARROW

Issue no: 1 Issue date: 09.11.07 Issued by: Standards Unit, Evaluations and Standards Laboratory Page no: 9 of 16
BSOP 38i1

This SOP should be used in conjunction with the series of other SOPs from the Health Protection Agency

www.evaluations-standards.org.uk

Email: standards@hpa.org.uk

4.4.3 CULTURE MEDIA, CONDITIONS AND ORGANISMS

| Clinical details/ conditions | Standard media | Incubation | | | Cultures read | Target organism(s) |
|---------------------------------|---|------------|-------------------------|--|--------------------------|-----------------------|
| | | Temp °C | Atmosphere | Time | | |
| All specimens | Blood culture broths (Subculture positive bottles as required) | 35 - 37 | Air | 7 d. Up to 21 d for slow growers + terminal subculture | Continuous monitoring | |
| | Chocolate agar | 35 - 37 | 5 – 10% CO ₂ | 40 - 48 h [*] | ≥ 40 h | Any organism |
| | Blood agar | 35 - 37 | 5 – 10% CO ₂ | 40 - 48 h | ≥ 40 h | |

Other organisms for consideration - *Mycobacterium* species (see [BSOP 40 - Investigation of specimens for Mycobacterium species](#)), fungi, and parasites (see [BSOP 31 - Investigation of specimens other than blood for parasites](#))

^{*}Incubation times may be increased up to 5 days if *Brucella* infections are suspected³⁵

4.5 IDENTIFICATION

4.5.1 MINIMUM LEVEL

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.

4.5.2 REFERRAL TO REFERENCE LABORATORIES

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

INVESTIGATION OF BONE MARROW

Issue no: 1 Issue date: 09.11.07 Issued by: Standards Unit, Evaluations and Standards Laboratory Page no: 10 of 16
BSOP 38i1

This SOP should be used in conjunction with the series of other SOPs from the Health Protection Agency

www.evaluations-standards.org.uk

Email: standards@hpa.org.uk

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 6AU
<http://www.thehtd.org/content/parasitology.asp>

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.

4.6 ANTIMICROBIAL SUSCEPTIBILITY TESTING

Refer to NSM on Susceptibility Testing (see [BSOP 45 - Susceptibility Testing](#))

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 – 72 h

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 – 72 h stating, if appropriate, that a further report will be issued.

5.3 ANTIMICROBIAL SUSCEPTIBILITY TESTING

Report susceptibilities as clinically indicated.

INVESTIGATION OF BONE MARROW

6 REPORTING TO THE HPA³⁶ (LOCAL AND REGIONAL SERVICES AND CENTRE FOR INFECTIOUS DISEASES)

Refer to the following:

Individual SOPs on organism identification

Health Protection Agency publications:

"Reporting to the CDR : A guide for diagnostic laboratories"

"Hospital infection control: Guidance on the control of infection in hospitals"

Refer to current guidance on CDSC and COSURV reporting

Local guidelines

Report all isolates of the following:

Mycobacterium species

Salmonella Typhi

Brucella species

All dimorphic fungi

INVESTIGATION OF BONE MARROW

Issue no: 1 Issue date: 09.11.07 Issued by: Standards Unit, Evaluations and Standards Laboratory Page no: 12 of 16
BSOP 38i1

This SOP should be used in conjunction with the series of other SOPs from the Health Protection Agency

www.evaluations-standards.org.uk

Email: standards@hpa.org.uk

7 ACKNOWLEDGEMENTS AND CONTACTS

This National Standard Method has been developed, reviewed and revised by the National Standard Methods Working Group for Clinical Bacteriology (http://www.hpa-standardmethods.org.uk/wg_bacteriology.asp). The contributions of many individuals in clinical bacteriology laboratories and specialist organisations who have provided information and comment during the development of this document, and final editing by the Medical Editor are acknowledged.

The National Standard Methods are issued by Standards Unit, Evaluations and Standards Laboratory, Centre for Infections, Health Protection Agency London.

For further information please contact us at:

Standards Unit
Evaluations and Standards Laboratory
Centre for Infections
Health Protection Agency
Colindale
London
NW9 5EQ
E-mail: standards@hpa.org.uk

INVESTIGATION OF BONE MARROW

Issue no: 1 Issue date: 09.11.07 Issued by: Standards Unit, Evaluations and Standards Laboratory Page no: 13 of 16
BSOP 38i1

This SOP should be used in conjunction with the series of other SOPs from the Health Protection Agency

www.evaluations-standards.org.uk

Email: standards@hpa.org.uk

REFERENCES

1. Department of Health NHS Executive: The Caldicott Committee. Report on the review of patient-identifiable information. London. December 1997.
2. Volk EE, Miller ML, Kirkley BA, Washington JA. The diagnostic usefulness of bone marrow cultures in patients with fever of unknown origin. *Am J Clin Pathol* 1998;110:150-3.
3. Woods GL, Gutierrez Y, Walker D H, Purtilo D T, Shanley J D, editors. *Diagnostic Pathology of Infectious Diseases*. Philadelphia: Lea and Febiger; 1993. p. 580
4. Riley UB, Crawford S, Barrett SP, Abdalla SH. Detection of mycobacteria in bone marrow biopsy specimens taken to investigate pyrexia of unknown origin. *J Clin Pathol* 1995;48:706-9.
5. Gotuzzo E, Carrillo C. *Brucella*. In: Gorbach SL, Bartlett JG, Blacklow NR, editors. *Infectious Diseases*. 2nd ed. Philadelphia: WB Saunders Company; 1998. p. 1837-45.
6. Shere KD, Goldberg MB, Rubin RH. Salmonella infections. In: Gorbach SL, Bartlett JG, Blacklow NR, editors. *Infectious Diseases*. 2nd ed. Philadelphia: WB Saunders Company; 1998. p. 699-712.
7. Gilman RH, Termini M, Levine MM, Hernandez-Mendoza P, Hornick RB. Relative efficacy of blood, urine, rectal swab, bone-marrow, and rose- spot cultures for recovery of Salmonella typhi in typhoid fever. *Lancet* 1975;1:1211-3.
8. Gotuzzo E, Carrillo C, Guerra J, Llosa L. An evaluation of diagnostic methods for brucellosis--the value of bone marrow culture. *J Infect Dis* 1986;153:122-5.
9. Moyer NP, Holcomb LA. Brucella. In: Murray PR, Baron EJ, Pfaller MA, Tenover FC, Tenover FC, editors. *Manual of Clinical Microbiology*. 6th ed. Washington: ASM; 1995. p. 549-55.
10. Guerra-Caceres JG, Gotuzzo-Herencia E, Crosby-Dagnino E, Miro-Quesada M, Carrillo-Parodi C. Diagnostic value of bone marrow culture in typhoid fever. *Trans R Soc Trop Med Hyg* 1979;73:680-3.
11. Brown KE. Parvovirus B19. In: Mandell GL, Bennett JE, Dolin R, editors. *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases*. 6th ed. Edinburgh: Churchill Livingstone; 2005. p. 1891-8.
12. Raoult D, Vestris G, Enea M. Isolation of 16 strains of Coxiella burnetii from patients by using a sensitive centrifugation cell culture system and establishment of the strains in HEL cells. *J Clin Microbiol* 1990;28:2482-4.
13. Wain J, Pham VB, Ha V, Nguyen NM, To SD, Walsh AL, et al. Quantitation of bacteria in bone marrow from patients with typhoid fever: relationship between counts and clinical features. *J Clin Microbiol* 2001;39:1571-6.
14. Advisory Committee on Dangerous Pathogens. 2004 Approved List of Biological Agents. <http://www.hse.gov.uk/pubns/misc208.pdf>. p. 1-17.
15. Public Health Laboratory Service Standing Advisory Committee on Laboratory Safety. *Safety Precautions: Notes for Guidance*. 4th ed. London: Public Health Laboratory Service (PHLS); 1993.
16. Control of Substances Hazardous to Health Regulations 2002. General COSHH. Approved Code of Practice and Guidance, L5. Suffolk: HSE Books; 2002.

INVESTIGATION OF BONE MARROW

Issue no: 1 Issue date: 09.11.07 Issued by: Standards Unit, Evaluations and Standards Laboratory Page no: 14 of 16
BSOP 38i1

This SOP should be used in conjunction with the series of other SOPs from the Health Protection Agency

www.evaluations-standards.org.uk

Email: standards@hpa.org.uk

17. Health and Safety Executive. 5 steps to risk assessment: a step by step guide to a safer and healthier workplace, IND (G) 163 (REVL). Suffolk: HSE Books; 2002.
18. Roberts LJ, Handman E, Foote SJ. Science, medicine, and the future: Leishmaniasis. *BMJ* 2000;321:801-4.
19. WHO. The leishmaniasis and Leishmania/HIV co-infections. WHO. <http://www.who.int/mediacentre/factsheets/fs116/en/index.html>.
20. Centers for Disease Control and Prevention. Leishmaniasis. www.dpd.cdc.gov.
21. Supparatpinyo K, Khamwan C, Baosoung V, Nelson KE, Sirisanthana T. Disseminated *Penicillium marneffe* infection in southeast Asia. *Lancet* 1994;344:110-3.
22. Deepe GS. *Histoplasma capsulatum*. In: Mandell GL, Bennett JE, Dolin R, editors. *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases*. 6th ed. Edinburgh: Churchill Livingstone; 2005. p. 3012-25.
23. Restrepo A, Tobon AM. *Paracoccidioides brasiliensis*. In: Mandell GL, Bennett JE, Dolin R, editors. *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases*. 6th ed. Edinburgh: Churchill Livingstone; 2005. p. 3062-8.
24. Hospenthal DR. Uncommon fungi. In: Mandell GL, Bennett JE, Dolin R, editors. *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases*. 6th ed. Edinburgh: Churchill Livingstone; 2005. p. 3068-79.
25. Sirisanthana T. Infection due to *Penicillium marneffe*. *Ann Acad Med Singapore* 1997;26:701-4.
26. Pintado V, Martin-Rabadan P, Rivera ML, Moreno S, Bouza E. Visceral Leishmaniasis in Human Immunodeficiency Virus (HIV)-Infected and Non-HIV-Infected Patients A Comparative Study. *Medicine (Baltimore)* 2001;80:54-73.
27. Health and Safety Executive. A guide to risk assessment requirements: common provisions in health and safety law, IND (G) 218 (L). Suffolk: HSE Books; 2002.
28. Health Services Advisory Committee. *Safety in Health Service Laboratories. Safe working and the prevention of infection in clinical laboratories and similar facilities*. 2nd ed. Suffolk: HSE Books; 2003.
29. NHS Estates. *Health Building Note 15. Facilities for pathology services*. 2nd ed. London: The Stationary Office; 2005.
30. BS EN 12469: 2000. *Biotechnology - performance criteria for microbiological safety cabinets*. London: British Standards Institution (BSI); 2000.
31. BS 5726: 1992. *Microbiological safety cabinets. Part 2. Recommendations for information to be exchanged between purchaser, vendor and installer and recommendations for installation*. London: British Standards Institution (BSI); 1992.
32. BS 5726: 1992. *Microbiological safety cabinets. Part 4. Recommendations for selection, use and maintenance*. London: British Standards Institution (BSI); 1992.
33. Advisory Committee on Dangerous Pathogens. *The management, design and operation of microbiological containment laboratories*. Suffolk: HSE Books; 2001.
34. Martin PK, Rowley JD. The effect of refrigeration of bone marrow and peripheral blood on cytogenetic analysis. *In Vitro Cell Dev Biol* 1986;22:387-91.

INVESTIGATION OF BONE MARROW

Issue no: 1 Issue date: 09.11.07 Issued by: Standards Unit, Evaluations and Standards Laboratory Page no: 15 of 16
BSOP 38i1

This SOP should be used in conjunction with the series of other SOPs from the Health Protection Agency

www.evaluations-standards.org.uk

Email: standards@hpa.org.uk

35. Durmaz G, Us T, Aydinli A, Kiremitci A, Kiraz N, Akgun Y. Optimum detection times for bacteria and yeast species with the BACTEC 9120 aerobic blood culture system: evaluation for a 5-year period in a Turkish university hospital. *J Clin Microbiol* 2003;41:819-21.
36. Health Protection Agency. Laboratory Reporting to the Health Protection Agency. Guide for diagnostic laboratories. February. 2007.

INVESTIGATION OF BONE MARROW

Issue no: 1 Issue date: 09.11.07 Issued by: Standards Unit, Evaluations and Standards Laboratory Page no: 16 of 16
BSOP 38i1

This SOP should be used in conjunction with the series of other SOPs from the Health Protection Agency

www.evaluations-standards.org.uk

Email: standards@hpa.org.uk