Monograph

on

Aspergillus and Aspergillosis
in man, animals and birds

A guide for classification and identification of aspergilli, diseases caused by them, diagnosis and treatment

By

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Preface

When Micheli in 1729 discovered the Aspergillus fungus, he had not expected that this fungus would continue for more than two and half centuries to be a subject of research, economic and medical interest. Species of the genus *Aspergillus*, like *Aspergillus oryzae*, have long been used in the manufacture of citric acid, soy sauce and other useful products. On the other hand, other species, like *Aspergillus flavus*, are known to produce highly toxic and carcinogenic substances in the foodstuffs they infest. Moreover, other species like *Aspergillus fumigatus*, cause disease in humans, animals and birds.

By the time Thom and Church published the first major monograph on the genus in 1926, *Aspergillus* had become one of the best-known and most studied mould groups. Their prevalence in the natural environment, their ease of cultivation on laboratory media and the economic importance of several of its species ensured that many mycologists and industrial microbiologists were attracted to their study. Now we are speaking of a genus, which is subdivided into sub-genera comprising sections and more than 250 species. The use of molecular biology in the study of *Aspergillus* has resulted in the moving of species from one subgenus to the other and from one section to the other. Some species are considered synonyms and some variants attained the status of a species. Such changes occur in short periods, so that one needs frequent updating to his knowledge.

Since I came back from Germany in 1965 after finishing my mycology study, I depended on the 3 identification keys of the *Aspergillus* species based on colours and micromorphology and we were satisfied to identify the groups of *Aspergillus*. Now it becomes difficult, as many species cannot be identified on their morphological basis, but need molecular biological techniques. This is why my post-graduate students become confused and asked me to prepare a lecture to simplify the matter. When I started to collect data for the lecture, I was drowned in a sea of information’s about this fungus. The enormous data which accumulated on my desk during the last 4 months encouraged me to write a monograph and upload it on my site in the internet to be available to all students, not only in Egypt, but in other parts of the world as well.

This monograph is dedicated to my supervisors, Prof. Dr.Dr. h.c. Kurt Wagener and Prof. Bisping who introduced me to the eminent mycologists of Europe, when they allowed me to accompany them, few months after arriving Germany in April 1962, to Travemuende on the Baltic Sea, to attend a meeting of mycology held on a ship. There I met Prof. Rieth, who invited me in his laboratory for one year. Prof. Rieth was fond of photographing fungi and writing teaching materials on all aspects of mycology.
<table>
<thead>
<tr>
<th>Item</th>
<th>Page</th>
<th>Item</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contents</td>
<td></td>
<td>6. Aspergillosis in animals</td>
<td>91</td>
</tr>
<tr>
<td>Preface</td>
<td>1</td>
<td>6.1. Aspergillosis in dogs</td>
<td>91</td>
</tr>
<tr>
<td>1. Introduction</td>
<td>4</td>
<td>6.2. Aspergillosis in cats</td>
<td>94</td>
</tr>
<tr>
<td>2. Historical</td>
<td>5</td>
<td>6.3. Aspergillosis in horses</td>
<td>96</td>
</tr>
<tr>
<td>4. Description of important aspergilli</td>
<td>17</td>
<td>6.5. Aspergillosis in Sheep and goats</td>
<td>100</td>
</tr>
<tr>
<td>4.1. Aspergillus Section Restriicti</td>
<td>17</td>
<td>6.6. Aspergillosis in pigs</td>
<td>104</td>
</tr>
<tr>
<td>4.2. Aspergillus Section Cervini</td>
<td>18</td>
<td>6.7. Aspergillosis in camels</td>
<td>104</td>
</tr>
<tr>
<td>4.5. Aspergillus section Usti</td>
<td>25</td>
<td>6.10. Aspergillosis in deers</td>
<td>106</td>
</tr>
<tr>
<td>4.6. Aspergillus section Versiclores</td>
<td>26</td>
<td>6.11. Aspergillosis in rabbits</td>
<td>107</td>
</tr>
<tr>
<td>4.9. Aspergillus section Terrei</td>
<td>35</td>
<td>7. Aspergillosis in birds</td>
<td>110</td>
</tr>
<tr>
<td>4.10. Aspergillus Section: Circumdati</td>
<td>39</td>
<td>7.1. Aspergillosis in poultry</td>
<td>110</td>
</tr>
<tr>
<td>4.11. Section: Flavipes</td>
<td>36</td>
<td>7.2. Aspergillosis in wild birds:</td>
<td>112</td>
</tr>
<tr>
<td>4.13. Aspergillus Section: Cremei</td>
<td>45</td>
<td>7.2.2. Aspergillosis in parrots</td>
<td>114</td>
</tr>
<tr>
<td>4.14. Aspergillus section Fumigati</td>
<td>46</td>
<td>7.2.3. Aspergillosis in quails</td>
<td>115</td>
</tr>
<tr>
<td>4.15. Aspergillus Section: Clavati</td>
<td>49</td>
<td>7.2.4. Aspergillosis in ostrich</td>
<td>116</td>
</tr>
<tr>
<td>4.16. Aspergillus Section: Nidulantes</td>
<td>50</td>
<td>7.2.5. Aspergillosis in red-tailed hawk</td>
<td>117</td>
</tr>
<tr>
<td>4.17. Aspergillus Section: Ornati</td>
<td>52</td>
<td>7.2.6. Aspergillosis in Red-billed Toucan</td>
<td>117</td>
</tr>
<tr>
<td>4.18. Aspergillus sect. Aeni</td>
<td>52</td>
<td>7.2.7. Aspergillosis in Snow Owl</td>
<td>118</td>
</tr>
<tr>
<td>5. Aspergillosis in man</td>
<td>78</td>
<td>7.2.8. Aspergillosis in Goshawk</td>
<td>118</td>
</tr>
<tr>
<td>5.1. Pulmonary aspergillosis</td>
<td>71</td>
<td>7.2.9. Aspergillosis in Cormorants</td>
<td>119</td>
</tr>
<tr>
<td>5.2. Cerebral aspergillosis</td>
<td>73</td>
<td>7.2.10. Aspergillosis in swans</td>
<td>119</td>
</tr>
<tr>
<td>5.3. Cutaneous aspergillosis</td>
<td>73</td>
<td>7.2.11. Aspergillosis in kiwi</td>
<td>120</td>
</tr>
<tr>
<td>5.4. Aspergillus Onychomycosis</td>
<td>75</td>
<td>8. Laboratory diagnosis of aspergillosis</td>
<td>123</td>
</tr>
<tr>
<td>5.5. Ocular aspergillosis</td>
<td>76</td>
<td>8.1. Direct microscopic examination</td>
<td>123</td>
</tr>
<tr>
<td>5.6. Aspergillus sinusitis</td>
<td>78</td>
<td>8.2. Isolation and identification</td>
<td>128</td>
</tr>
<tr>
<td>5.7. Paranasal sinuses aspergillosis</td>
<td>79</td>
<td>8.3. Molecular identification of aspergilli</td>
<td>132</td>
</tr>
<tr>
<td>5.8. Otoaspergillosis</td>
<td>81</td>
<td>8.4. Serological techniques</td>
<td>135</td>
</tr>
<tr>
<td>5.9. Aspergillus endocarditis</td>
<td>82</td>
<td>9. Treatment of aspergillosis</td>
<td>140</td>
</tr>
<tr>
<td>5.10. Aspergillus thyroiditis</td>
<td>84</td>
<td>10. References</td>
<td>143</td>
</tr>
<tr>
<td>5.11. Hepatic aspergillosis</td>
<td>85</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1. Introduction

Aspergillus is one of the oldest named genera of fungi that received its name from Micheli in 1729. In viewing the microscopic spore-bearing structure, Micheli was reminded of a device used by the Roman Catholic clergy to sprinkle holy water during a part of the liturgy called the asperges (Ainsworth, 1976). The asperges was described as follows in the 11th edition of The Encyclopedia Britannica:

**ASPERGES** (*'thou wilt sprinkle,' from the Latin verb aspergere*), the ceremony of the Roman Catholic Church ... with which the priest begins the ceremony. The brush used for sprinkling is an aspergill (aspergillum)... (Anonymous, 1910)

![Aspergillum](image)

Aspergillum: a brush or small perforated container with a handle that is used for sprinkling holy

The aspergillum-like spore-bearing structure is the most important microscopic character used in defining members of the genus *Aspergillus*. During mycelial differentiation certain cells enlarge, develop a heavy cell wall and form 'T' or 'L' shaped 'foot cells', which are not separate cells and that produce a single conidiophore perpendicular to the long axis of the cell. The erect hyphal branch developing from the foot cell is the conidiophore, which enlarges at its apex to form a rounded, elliptical or club shaped vesicle. The fertile area of the vesicle gives rise to a layer of cells called phialides (sterigmata) that produce long chains of mitotic spores called conidia or conidiospores. The size and arrangement of the conidial heads as well as the colour of the spores they bear are important identifying characteristics.
2. Historical

2.1. 1729-1809

- **Pier Antonio Micheli** was not only a Catholic Priest but also a famous botanist. His *Nova plantarum genera* of 1729 was a milestone in the study of fungi. In this work, with descriptions of 1900 plants, including new 1400, he described 900 fungi and lichens. Micheli gave the name Aspergillus (rough head) and described *Aspergillus capitatus ochroleucus*, probably some strains of *Aspergillus ochraceus*; *Aspergillus capilulo pulla* for a black form, etc.
2.2. 1809-1926

- **Link (1809)** described *A. glaucus. Aspergillus candidus, Aspergillus chevalieri, Aspergillus flavus* and *Eurotium herbariorum*
- **Corda (1828)** published his studies of fresh material, as seen under his microscope. He described several species, e.g. *Aspergillus phoenicis, Aspergillus repens*
- **Desmazières (1834)** described *A. clavatus*
- **DeBary (1854)** noticed that an *Aspergillus* mycelium could produce a cleistothecium as well as an aspergillum. Cleistothecium-producing mould had been observed before and given its own name: *Eurotium herbariorum*. DeBary realized that *A. glaucum* and *E. herbariorum* were different reproductive phases of the same organism, thus putting the dual naming of the same fungus in its sexual and asexual stages.
• Fresenius (1863) described *Aspergillus fumigatus* and *Sterigmatocystis sulphurea*
• Berk. & M. A. Curtis (1868) described *Aspergillus erythrocephalis*
• van Tieghem (1867) described *Aspergillus niger*
• Wilhelm (1877) described *Aspergillus ochraceus*
• Ahlburg (1878) described *Eurotium oryzae*
• Bainier (1880-1913) described *A. ustus, A. flavipes, Sterigmatocystis usta, Sterigmatocystis flavipes, Sterigmatocystis sydowii, Aspergillus gracilis* and *Sterigmatocystis carbonaria*
• Saccardo (1882) described *A. repens*
• Eidam (1883) described *Sterigmatocystis nidulans*
• Winter (1884) described *A. nidulans*
• Cohn (1884) described *Aspergillus oryzae*
• Gasperini (1887) described *Aspergillus elegans, Aspergillus violaceofuscus*
• Delacroix (1893) described *Aspergillus brunneus, Eurotium echinulatum*
• Wehmer (1896-1907) devided the genus Aspergillus in Subgenus Microaspergillus and Macroaspergillus. He described Aspergillus ostianus, Aspergillus wentii, Aspergillus fischeri, Aspergillus giganteus, Aspergillus sulphureus, Aspergillus varians, Aspergillus pulverulentus*
• Höhn (1902) described *Aspergillus citriscopus*
• Vuillemin (1903-1908) *Sterigmatocystis versicolor, Aspergillus versicolor*
• Saito (1904-1906) described *Aspergillus caesiellus, Aspergillus japonicus*
• Mangin (1909-1910) described *Aspergillus chevalieri, Eurotium chevalieri*
• Yukawa (1911) described *Aspergillus melleus*
• Kita (1913) described *Aspergillus tamarii*
• Blochwitz (1914) described *Aspergillus conicus*
• Massee (1914) described *Aspergillus cervinus*
• Thom and Church (1918) described *A. terreus*
2.3. 1926-1965

- **Thorn and Church (1926)** revised some 350 names, but only 69 species were accepted, which were more or less arbitrarily considered in 11 groups. Their studies resulted in the publication in the 1926 of a monograph entitled “The Aspergilli.”

They based their taxonomy of the macroscopic colony characters and the microscopic features of the vesicles, conidiophores, the single or double series of the spore-bearing phialides and the shapes and colours of conidia.

- **Thom and Raper (1945)** used the work of Thorn and Church as a basis for subsequent taxonomic treatments of the genus in their book entitled “A Manual of the Aspergilli”. They classified the Aspergillus species into 14 groups and 9 series.

- **Raper & Fennell (1965)** described 150 taxa in their monograph “The Genus Aspergillus”. They divided the species into 18 informal “groups” based on the authors’ opinions of probable relationships. These groups contained 132 species and 18 varieties.
2.4. 1965-2011

- **Gams et al (1985)** replaced the groups by sections and divided the genus *Aspergillus* into 18 sections organized in six subgenera.
- **Pitt et al. (2000)**, in their latest compilation of names in current use, listed 182.
- **Samson (2000)** listed another 36 published between 1992 and 1999. More than 40 new species descriptions have been published since then, bringing the total number to ~250.
- **Samson, R.A., and Varga, J.(2007)**, in their book *Aspergillus* systematics in the genomic era, they presented the activities the workshop held on 12-14 April, 2007 at the CBS, Fungal Biodiversity Centre, Utrecht – The Netherlands covering the following themes:
  - What is the impact of Aspergillus taxonomy in terms of epidemiology, case definitions and biological understanding of disease?
  - What and how many genes should be used to delimit an Aspergillus taxon?
  - How does the phylogenetic species concept translate to practical and routine diagnoses?
  - What are the roles of Aspergillus databases for species identification?
  - What is the value and impact of polyphasic approaches for species identification?
  - What genes/methods can be used to design kits for rapid identification?
  - How should new species be proposed?
• **Geiser et al. (2008)** mentioned that there are approximately 250 named species of *Aspergillus* and this number is likely to increase significantly in the near future because of increasing application of the phylogenetic species concept based on DNA sequence data rather than on visible morphological characters.


• **M. Machida and K. Gomi (2010)** published their book “Aspergillus, molecular biology and genomics” summarized the most important aspects of Aspergillus molecular biology and genomics.

3. Nomenclature and classification

- During the 20th century, as mycologists isolated and identified increasing numbers of isolates, the number of named species of *Aspergillus* increased. These tended to fall into morphologically distinct clusters. So in order to facilitate identification, the genus was divided into intrageneric 'groups'. The *Aspergillus glaucus* group, for example, was characterized by abundant, typically green conidial heads, with perithecia generally present, while the *Aspergillus ochraceous* group had yellow conidia and abundant cream to purplish-coloured sclerotia.

- The term 'group' does not have nomenclatural status within the formal rules of biological nomenclature. Therefore, the genus was reorganized into a new subgeneric taxonomic hierarchy based on 'sections.' In this system, The genus was subdivided into subgenera.

- The subgenus 'Aspergillus' consists of xerophilic species. *A. glaucus* is the type species, classified in the subgenus *Aspergillus* and the section *Aspergillus*.

- A new subgenus was introduced called Circumdata that encompassed seven sections, in which 'section circundati' was the new rubric for the old 'A. ochraceous group'. The attempted imposition of subgeneric epithets, only one of which is called 'Aspergillus' is extremely confusing and has not caught on. On the other hand, most taxonomists now use
the term 'section' rather than 'group' for *Aspergillus* intrageneric classifications and identifications.

- Some *Aspergillus* species regularly produce both sexual and asexual spores; in other species the sexual form is rare; for still others, sexual spores have never been seen - and perhaps never will be seen.
- The names used for currently accepted sexual genera with close phylogenetic relationship or known linkage to *Aspergillus* species (representative *Aspergillus* species given in parenthesis) are:

1. Chaetosartorya (*A. wentii*);
2. Emericella (*A. nidulans*);
3. Eurotium (*A. glaucus*);
4. Fennellia (*A. terreus*);
5. Hemicarpenteles (*A. paradoxus*);
6. Neocarpenteles (*A. clavatus*);
7. Neosartorya (*A. fumigatus*);
8. Petromyces (*A. flavus*);
9. Sclerocleista (*A. ornatus*);
10. Warcupiella (*A. spinnulosus*).

### 3.1. Classification according to Thom and Raper (1945)

Thom and Raper (1945) classified the *Aspergillus* species into 14 groups and 9 series as follows:

**Group 1: THE ASPERGILLUS CLAVATUS GROUP**

**Group 2: THE ASPERGILLUS GLAUCUS GROUP**

1. ASPERGILLUS REPENS SERIES
2. ASPERGILLUS RUBER SERIES
3. ASPERGILLUS CHEVALIERI SERIES
4. ASPERGILLUS AMSTELODAMI SERIES
5. ASPERGILLUS RESTRICUTUS SERIES

**Group 3: THE ASPERGILLUS FUMIGATUS GROUP**

6. ASPERGILLUS FUMIGATUS SERIES
7. ASPERGILLUS FISCHERI SERIES

**Group 4: THE ASPERGILLUS NIDULANS GROUP**

**Group 5: THE ASPERGILLUS USTUS GROUP**

**Group 6: THE ASPERGILLUS FLAVIPES GROUP**
Group 7: THE ASPERGILLUS VERSICOLOR GROUP  
Group 8: THE ASPERGILLUS TERREUS GROUP  
Group 9: THE ASPERGILLUS CANDIDUS GROUP  
Group 10: THE ASPERGILLUS NIGER GROUP

8. ASPERGILLUS NIGER SERIES  
9. ASPERGILLUS CARBONARIUS SERIES

Group 11: THE ASPERGILLUS WENTII GROUP  
Group 12: THE ASPERGILLUS TAMARII GROUP  
Group 13: THE ASPERGILLUS FLAVUS-ORYZAE GROUP  
Group 14: THE ASPERGILLUS OCHRACEUS GROUP

### 3.2. Classification according to Raper and Fennel (1965)

Raper and Fennel (1965) divided species into 18 informal “groups”, which contained 132 species and 18 varieties as follows:

### 3.3. Classification according to Gams, Christensen, Onions, Pitt and Samson

Gams et al (1985) replaced the groups by sections and divided the genus *Aspergillus* into 18 sections organized in six subgenera.

<table>
<thead>
<tr>
<th>Subgenera</th>
<th>Sections (Gams et al., 1985)</th>
<th>Groups (Raper &amp; Fennel, 1965)</th>
</tr>
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</table>
| *Aspergillus* | Aspergillus  
Restricti  
Fumigati  
Ornati  
Clavati  
Nidulantes  
Versicolor  
Usti  
Terrei  
Flavipes  
Wentii  
Flavi  
Nigri  
Circumdati  
Candidi  
Cremei  
Sparsi | A. glaucus  
A. restrictus  
A. fumigatus  
A. cervinus  
A. ornatus  
A. clavatus  
A. nidulans  
A. versicolor  
A. ustus  
A. terreus  
A. flavipes  
A. wentii  
A. flavus  
A. niger  
A. ochraceus  
A. candidus  
A. cremeus  
A. sparsus |
They then added the teleomorph names as follows:

1. **Subgenus Aspergillus**
   1. Section: Aspergillus (Teleomorph: Eurotium)
   2. Section: Restricti

2. **Subgenus Circumdati**
   3. Section: Circumdati (Teleomorph: Neopetromyces)
   4. Section: Nigri
   5. Section: Flavi (Teleomorph: Petromyces)
   6. Section: Cremei (Teleomorph: Chaetosartorya)
   7. Section: Candidi
   8. Section: Wentii
   9. Section: Sparsi

3. **Subgenus Clavati**
   10. Section: Clavati (Teleomorph: Neocarpenteles)

4. **Subgenus Fumigati**
   11. Section: Cervini
   12. Section: Fumigati (Teleomorph: Neosartorya)

5. **Subgenus Nidulantes**
   13. Section: Nidulantes (Teleomorph: Emericella)
   14. Section: Versicolores
   15. Section: Flavipes (Teleomorph: Fennellia)
   16. Section: Usti
   17. Section: Terrei (Teleomorph: Fennellia)

6. **Subgenus Ornati**
   18. Section: Ornati (Teleomorph: Sclerocleista)
3.4. Classification according Petron (2000)

Peterson (2000) reported that phylogenetic studies of ribosomal RNA gene sequences led to the acceptance of 3 subgenera with a total of 16 sections and the so-called »Warcupiella group«, a treatment currently accepted by most Aspergillus researchers:

**Subgenus Aspergillus**

1. Section: Aspergillus (Teleomorph: Eurotium)
2. Section: Restricti
3. Section: Cervini
4. Section: Terrei (Teleomorph:Fennellia)
5. Section: Flavipes (Teleomorph:Fennellia)
6. Section: Nigri
7. Section: Circumdati (Teleomorph:Neopetromyces)
8. Section: Flavi (Teleomorph:Petromyces)
9. Section: Cremei (Teleomorph:Chaetosartorya)
10. Section: Candidi

**Subgenus Fumigati**

11. Section:Fumigati (Teleomorph:Neosartorya)
12. Section:Clavati (Teleomorph:Neocarpenteles)

**Subgenus Nidulantes**

13. Section:Nidulantes (Teleomorph:Emericella)
14. Section:Usti
15. Section:Versicolores
16. Section:Ornati (Teleomorph:Hemicarpenteles)

3.5. Molecular classification of Aspergillus and its Teleomorphs

Based on the phylogenetic analysis of multilocus (calmodulin, RNA polymerase 2 and rRNA) sequence data (Samson and Varga, 2009 and Varga et al. 2010), Aspergillus can be subdivided into eight subgenera and 19 sections as follows:

1. **Subgenus Aspergillus**
   1. Sections Aspergillus
   2. Sections Restricti;
2. **Subgenus Fumigati**
   3. Sections Fumigati
   4. Sections Clavati
   5. Sections Cervini
3. **Subgenus Circumdati**
   6. Sections Circumdati

15
7. Sections Nigri
8. Sections Flavi
9. Sections Cremei
10. Aspergillus sect. Aeni sect. nov

4. Subgenus Candidi
   11. Section Candidi;

5. Subgenus Terrei
   12. Sections Terrei
   13. Sections Flavipedes;

6. Subgenus Nidulantes
   14. Sections Nidulantes
   15. Sections Usti
   16. Sections Sparsi;

7. Subgenus Warcupi
   17. Sections Warcupi
   18. Sections Zonati

8. Subgenus Ornati
   19. Sections Ornati.


It is suggested to divide the Genus Aspergillus into 2 Subgenera:

1. **Subgenus I** contains 6 Aspergillus sections that have no known teleomorphs yet, namely Sections Restricti, Cervini, Nigri, Candidi, Usti and Versicolores.

2. **Subgenus II** contains 10 aspergillus sections that have teleomorphs, namely Sections Aspergilli, Terrei, Flavipes, Circumdati, Flavi, Cremei, Fumigati, Clavati, Nidulantes and Ornati.

3. **The name Michelius** or **Michelia** is suggested as the genus name for all telemorphs, which is devided into the following sections: Euroti, Fennelli, Neopetromycei, Petromycei, Chaetosartori, Neosartori, Neocarpentelli, Emericelli and Hemicarpentelli.

Consequently, the species that have teleomorphs will be named as follows:

*Aspergillus glaucus*  **Link, 1809**
Teleomorph: *Michelia herbariorum*
Synonym: *Eurotium herbariorum* Link, 1809
4. Description of important aspergilli

4.1. Aspergillus Section Restricti

_Aspergillus_ Section _Restricti_ (the _Aspergillus restrictus_ Group) include the following species

1. _Aspergillus caesiellus_
2. _Aspergillus penicillioides_
3. _Aspergillus restrictus_
4. _A. conicus_
5. _A. gracilis_
6. _A. itaconicus_

4.1.1. _Aspergillus restrictus_ G. Smith (1931)

Synonym: _Penicillium fuscoflavum_ S. Abe (1956)

**Morphology** (http://www.bcrc.firdi.org.tw/fungi/fungal)

Colony diameters on Czapek’s Agar 1.3-1.5 cm in 2 weeks at 25°C, dense, rugged, floccose, with fimbriate margins; mycelium white; conidial heads small, indistinct, covered in slime, blackish green-gray; reverse uncolored to dark gray green. Colony diameters on M40Y 4.5-5.5 cm in 2 weeks at 25°C, velutinous, tufted or floccose; conidial heads long, narrow, columnar, sometimes twisted, artemisia green to lily green; reverse colorless to olive brown; vesicles flask shaped, or pyriform, 5.0-13.0 μm in diameter; stipes thin-walled, smooth or roughened, straight or sinuous, uncolored, 78-106 × 2.0-6.0 μm. Aspergilla uniseriate, phialides 4.8-10.3 × 2.4-4.4 μm, covering the upper 2/5 of the vesicle. Conidia elongate, doliiform or ellipsoidal to pyriform, 3.8-9.5 × 3.0-4.4 μm, rough to spinose.
4.2. Aspergillus Section Cervini

The section *Cervini* branch contains the four species placed in the group by Raper and Fennell (1965). Full congruence of trees based on the separate loci and strong statistical support recognize the six lineages. Isolates phenotypically identified as *A. kanagawaensis* and as *A. nutans* each split into two separate lineages (Peterson, 1980). The following are the species:

1. *Aspergillus kanagawaensis*
2. *Aspergillus nutans*
3. *Aspergillus cervinus*
4. *Aspergillus parvulus*
5. *A. kanagawaensis*
6. *A. nutans*

4.2.1. *Aspergillus cervinus* Massee, 1914

Fennell (1964) rediscovered *Aspergillus cervinus* as a uniseriate fawn-colored Aspergillus obtained from Malayan forest soils. The outstanding characteristics of this sp. are a fawn to pinkish-cinnamon surface color, thick-walled conidiophores up to 9.5[µm] wide, a single series of sterigmata borne radiately on the vesicle, and globose smooth conidia. The Malayan cultures and an obtained Wisconsin isolate matched in essential details Massee's original diagnosis and Neill's later description of *A. cervinus*. They appear to be the only extant representatives of the sp. The mold *Aspergillus cervinus* is considered to be rare, as it has only been isolated from the tropical rainforest soils of Malaya, Puerto Rico, Wisconsin, New Zealand and India.
4.3. Aspergillus section Nigri

Aspergillus section Nigri are industrially one of the most important taxa of filamentous fungi. Several strains belonging to this section are used in the fermentation industry for the production of different organic acids and hydrolytic enzymes.

- The observation that black aspergilli including A. niger and A. carbonarius are able to produce ochratoxins is economically important since A. niger is extensively used in the food industry.
- Taxonomic evaluation of this species complex was carried out using different methods (Varga et al., 2011). Among the genotypic approaches, nuclear and mtDNA polymorphisms and PCR based techniques led to the recognition of four species within this species complex (A. niger, A. tubingensis, A. brasiliensis, A. foetidus).
- Several well known species names such as A. awamorii, A. usamii, A. phoenicis and A. ficuum have been reduced to synonymy.

- Regarding other black Aspergillus species, phylogenetic analysis of ITS sequence data indicates that at least 9 species belong to this section:
  1. Aspergillus heteromorphus,
  2. Aspergillus ellipticus,
  3. Aspergillus carbonarius,
  4. Aspergillus japonicus,
  5. Aspergillus aculeatus,
  6. Aspergillus niger,
  7. Aspergillus tubingensis,
  8. Aspergillus foetidus and

- Ochratoxin production has been observed only in A. niger and A. carbonarius isolates. These species are now considered as major sources of ochratoxin contamination in tropical and subtropical foods including dried vine fruits, wines and coffee.
- The identification of species of Aspergillus section Nigri depends on:
  a. Colony morphology, conidial size and ornamentation of the cultures
  b. The temperature range of all species
  c. Growth characteristics on creatine agar and boccalid agar.
  d. The extrolites produced by each species
  e. The response of the Ehrlich reaction
  f. Molecular characterization (β-tubulin or calmodulin sequence data)
4.3.1. *Aspergillus niger* van Tieghem 1867

Synonyms:  
*Sterigmatocystis nigra* (Tiegh.) Tieghem, (1877)  
*Aspergillopsis nigra* (Tiegh.) Speg., (1910)  
*Rhopalocystis nigra* (Tiegh.) Grove (1911)  
*Aspergillus pyri* W.H. English  
*Aspergillus fuliginosus* Peck, (1873)  
*Aspergillus cinnamomeus* E. Schiemann (1912)  
*Aspergillus fuscus* E. Schiemann (1912)  
*Aspergillus niger* var. altipes E. Schiemann, (1912)  
*Aspergillus schiemanni* Thom (1916)

**Morphology:**
On Czapek dox agar, colonies consist of a compact white or yellow basal felt covered by a dense layer of dark-brown to black conidial heads. Conidial heads are large (up to 3 mm x 15-20 um in diameter), globose, dark brown, becoming radiate and tending to split into several loose columns with age. Conidiophores are smooth-walled, hyaline or turning dark towards the vesicle. Conidial heads are biseriate with the phialides borne on brown, often septate metulae. Conidia are globose to subglobose (3.5-5.0 um in diameter), dark brown to black and rough-walled.

![Morphology images](image-url)
**A. niger** is one of the most common species of the genus *Aspergillus*. It causes a disease called black mold on certain fruits and vegetables such as grapes, onions, and peanuts, and is a common contaminant of food. It is ubiquitous in soil and is commonly reported from indoor environments,

1. *Aspergillus niger* can cause aspergillosis in man, in particular, frequent among horticultural workers that inhale peat dust, which can be rich in *Aspergillus* spores. It is one of the most common causes of otomycosis (fungal ear infections), which can cause pain, temporary hearing loss, and, in severe cases, damage to the ear canal and tympanic membrane.

2. Various strains of *Aspergillus niger* are used in the industrial preparation of citric acid and gluconic acid and have been assessed as acceptable for daily intake by the World Health Organisation. *A. niger* fermentation is "generally recognized as safe" (GRAS) by the United States Food and Drug Administration Many useful enzymes are produced using industrial fermentation of *Aspergillus niger*, e.g., *A. niger* glucoamylase, pectinases, Alpha-galactosidase and proteases.

3. *Aspergillus niger* growing from gold mining solution contained cyano metal complexes; such as gold, silver, copper iron and zinc. The fungus also plays a role in the solubilization of heavy metal sulfides. Alkali treated *Aspergillus niger* binds to silver to 10% of dry weight. Silver biosorption occurs via stoichiometric exchange with Ca(II) and Mg(II) of the sorbent.

4. In 2006, it was reported that a secreted RNase produced by *Aspergillus niger* called *actibind* has antiangiogenic and anticarcinogenic characteristics.

### 4.3.2. *Aspergillus carbonarius* (Bainier) Thom, (1916)

Synonyms:  
*Sterigmatocystis carbonaria* Bainier, (1880)  
*Rhopalocystis carbonaria* (Bainier) (1911)  
*Aspergillopsis puchella* Speg. (1910)  
*Aspergillopsis pulchella* Speg., (1910)  
*Aspergillus atropurpureus* (1902)  
*Sterigmatocystis acini-uvae* Caball., (1928)  
*Aspergillus fonsecaeus* Thom & Raper, (1965)

**Morphology**  
(http://www.bcrc.firdi.org.tw/fungi/fungal)  

Colony diameters on Czapek’s Agar 4.0-4.5 cm in 7 days at 25°C, basal mycelium white, velvety, marginal mycelium low; reverse white to dark grey; exudate clear to slight greyish yellow; conidial heads globose to radiate or rarely splitting into loose columns, deep olive or black; stipes 300-5720 × 6.4-31.5 μm, smooth to rough, thick-walled, uncolored to brown or
reddish brown towards the vesicle; vesicles globose to subglobose 20-96 μm in diameter. Aspergilla biseriate, metulae covering the upper 1/2 to the entire surface of the vesicle, 14.0-50.0 × 6.0-14.0 μm; phialides 8.0-12.0 × 5.0-8.0 μm. Conidia spherical, 5.6-12.0 μm in diameter, spinulose when young, tuberculate at maturity. Colony diameters on Malt Extract Agar 5.0-6.0 cm in 7 days at 25°C; conidial heads radiate to globose, or splitting into more or less well defined columns, blackish brown; reverse uncolored.

*Aspergillus carbonarius* resembles *A. niger* in many features, and indeed the two species are very closely related. *A. carbonarius* differs from *A. niger* most notably in the production of larger spores, although other minor morphological differences exist. The available information on its physiology indicates a broad similarity to *A. niger*. Recently, black aspergilli, mainly *Aspergillus carbonarius* and members of the *Aspergillus niger* aggregate, have been described as a main possible sources of ochratoxin (OTA) contamination in grapes from Argentina and Brazil, France, Italy, Spain, Portugal, Greece and Australia as well as in dried vine fruits from different origins. Strong evidence of the contribution of *A. carbonarius* to the OTA contamination of wine has been also reported. Ochratoxin A is a highly harmful metabolite classified in 1993 by the International Agency for Research on Cancer (IARC, 1993) as a possible human carcinogenic toxin (group 2B).
4.4. Aspergillus section Candidi

Aspergillus section Candidi historically included a single white-spored species, A. candidus. Later studies clarified that other species may also belong to this section. The revised section Candidi by Varga et al. (2007) includes 4 species:

1. candidus
2. campestris
3. taichungensis
4. tritici.

Morphological characteristics of section Candidi:

- Slow growing colonies with globose conidial heads having white to yellowish conidia, Conidiophores smooth, small conidiophores common, metulae present and covering the entire vesicle,
- Some large Aspergillus heads with large metulae,
- Presence of diminutive heads in all species,
- Conidia smooth or nearly so with a subglobose to ovoid shape,
- Presence of sclerotia in three species (A. candidus, A. taichungensis and A. tritici).
- All species produce terphenyllins and candidusins and three species (A. candidus, A. campestris and A. tritici) produce chlorflavonins. Xanthoascins have only been found in A. candidus.
- Each of the species in section Candidi produce several other species specific extrolites, and none of these have been found in any other Aspergillus species A. candidus has often been listed as a human pathogenic species, but this is unlikely as this species cannot grow at 37 °C.

4.4.1. Aspergillus candidus Link, (1809)

Synonyms: Aspergillus albus K. Wilh.
Aspergillus okazakii Saito, (1907)
Aspergillus albus var. thermophilus Nakaz., Takeda & Suematsu, (1932)
Aspergillus tritici B.S. Mehrotra & M. Basu, (1976)
Aspergillus triticus B.S. Mehrotra & M. Basu (1976)

Morphology (http://www.bcrc.firdi.org.tw/fungi/fungal
Colony diameters on Czapek’s Agar 1.5-1.7 cm in 14 days at 25°C, dense, plane; conidial heads radiate, white to ivory yellow; mycelium white; reverse white to cream color or warm buff to light ochraceous-buff, stipes 64-800 × 4.0-8.7 μm, hyaline, smooth; vesicles subglobose, globose, ellipsoidal or obovoid, 5.6-26.0 μm wide. Aspergilla biseriate, occasionally uniseriate; metulae 4.4-11.1 × 2.1-3.8 μm, usually swollen, covering the whole surface of the vesicle; phialides 5.8-10.6 × 2.5-3.6 μm. Conidia subglobose or globose to ellipsoidal, smooth, 2.2-3.7 μm wide. Colony diameters on Malt Extract Agar 1.8-2.2 cm in 14 days at 25°C, dense,
velutinous; conidial heads radiate, white to pale ivory; mycelium white; reverse ivory yellow to cream color.

**Aspergillus candidus**. Samson et al., 2011

- *Aspergillus candidus* is a common contaminant of grain dust and which causes respiratory disease in humans. The species is widely distributed in nature and develops upon vegetation in the later stages of decay. It has been reported from grain, flour, hay, compost and a fur processing facility.
- Growth of *A. candidus* on barley grain occurs at the substrate water content 20-25% and maximal temperature 30-40°C.
- *A. candidus* may produce citrinin and other mycotoxins. Also this species produces p-terphenyl metabolites and, which are potent cytotoxic substances.
- Some strains of *A. candidus* produce kojic acid and / or citrinin, molecules that can cause renal disease in swine.
- *A. candidus* is involved in various human infections: invasive aspergillosis, otomycosis, onychomycosis.
4.5. *Aspergillus* section *Usti*

Based on phylogenetic analysis of sequence data (Samson *et al.*, 2011), *Aspergillus* section *Usti* includes the following species:

1. *Aspergillus ustus*,
2. *Aspergillus puniceus*,
3. *Aspergillus granulosus*,
4. *Aspergillus pseudodeflectus*,
5. *Aspergillus calidoustus*,
6. *Aspergillus insuetus*
7. *A. compatibilis* (*Emericella heterothallica*)
8. *Aspergillus heterothallicus* (*Fennellia monodii*)
10. *Aspergillus germanicus* sp. nov. was isolated from indoor air in Germany. This species is unable to grow at 37 °C, similarly to *A. keveii* and *A. insuetus*.
11. *Aspergillus carlsbadensis* sp. nov. was isolated from the Carlsbad Caverns National Park in New Mexico. This species is also unable to grow at 37 °C, and acid production was not observed on CREA.
12. *Aspergillus californicus* sp. nov. is proposed for an isolate from chamise chaparral (*Adenostoma fasciculatum*) in California. This species grew well at 37 °C, and acid production was not observed on CREA.
13. *Aspergillus turkensis* sp. nov. was isolated from soil in Turkey. This species grew, although rather restrictedly at 37 °C, and acid production was not observed on CREA.
14. *Aspergillus pseudoustus* sp. nov. was isolated from stored maize, South Africa
15. *Aspergillus monodii* comb. Nov

4.5.1. *Aspergillus ustus* (Bainier) Thom & Church, 1924.

Synonyms: *Sterigmatocystis usta* Bainier (1881)

*Aspergillus humus* Abbott (1926)

*A. ustus* is a variable species. *A. ustus* isolates may vary in their colony colour from mud brown to slate grey, with colony reverse colours from uncoloured through yellow to dark brown. Colony diam, 7 d, in mm: CYA 36-43; CYA37 no growth; MEA25 39-46; YES 42-50. Colony texture: floccose, plane, sulcate or umbonate. Conidial head: radiate to hemispherical. Stipe: 400 × 3-6 μm, aerially borne stipes up to 125 × 2-5 μm, smooth, brownish. Vesicle diam/shape: 7-15 μm, hemispherical to subglobose. Conidium size/shape/surface texture: 3.2-4.5 μm, globose, roughened, greenish to dark yellow brown. Hülle cells: irregularly ovoid or elongate, usually scattered. Ehrlich reaction: no reaction. Growth on creatine: good growth with faint yellow mycelium, no acid production.
**Diagnostic features:** No growth at 37 °C; good growth on creatine with faint yellow pigmented mycelium; Hülle cells typically scattered or form irregular masses and not associated with pigmented mycelium.

4.6. *Aspergillus* section *Versicolores*

*Aspergillus* section *Versicolores* was originally erected as the *Aspergillus versicolor* group by Thom & Church (1926) and was subsequently revised by Thom & Raper (1945) to contain four species. Raper & Fennell (1965) revised the genus *Aspergillus* and accepted 18 species in the *A. versicolor* group. Gams *et al.* (1985) formalized the sectional taxonomy of Raper & Fennell’s (1965) groups. Peterson (2008) accepted four phylogenetically distinct species in the section based on multilocus DNA sequence analysis.

*Aspergillus versicolor* is the most widely reported and studied species in section *Versicolores*. It has been isolated from, indoor environments, various foods and feeds and hypersaline water, and is associated with many health issues of humans and animals. It is a producer of the mycotoxin sterigmatocystin that is a precursor of aflatoxin B$_1$.

The section *Versicolores* was revised by Jurjevic *et al.* (2012) and contains the following species:

1. *Aspergillus sydowii*,
2. *Aspergillus creber*,
3. *Aspergillus venenatus*,
4. *Aspergillus tennesseensis*,
5. *Aspergillus cvjetkovicii*,
6. *Aspergillus jensenii* and
7. *Aspergillus puulaaensis*;
8. *Aspergillus versicolor*,
9. *Aspergillus tabacinus*,
10. *Aspergillus fructus*,

Aspergillus ustus, Samson et al., 2011
11. Aspergillus protuberus,
12. Aspergillus amoenus and
13. Aspergillus. Austroafricanus

4.6.1. Aspergillus sydowii Thom & Church (1926)

Synonyms: Sterigmatocystis tunetana Langeron, (1924)
Aspergillus sydowii var. achlamydosporus Nakaz. et al. (1934)

When grown in pure culture on agar plates, A. sydowii produces blue-green colonies with reddish-brown shades. Colony on Czapek’s Agar is plane to floccose; conidial heads radiate to loosely columnar, light grayish olive or green; mycelium white; reverse ivory yellow or maroon; stipes hyaline to pale brown, smooth; vesicles clavate to subglobose. Aspergilla biseriate, metulae covering 1/2 to 4/5 of the vesicle; Conidia globose, conspicuously roughened to spinose. Small aspergilla often present resembling the fruiting structures of Penicillium. Hulle cells occasionally present, globose to subglobose.
Aspergillus sydowii is a saprophytic fungus found in soil that can contaminate food and is occasionally pathogenic to humans. It is the predominant fungus found on wheat *Qu*, the most widely used source of raw microorganisms and crude enzymes for Chinese rice wine brewing. Since the 1990s it has been found to be present in sea water in the Caribbean region and has been shown to be the cause of aspergillosis in sea fans.

*Aspergillus sydowii* has been implicated in the pathogenesis of several human diseases, including aspergillosis, onychomycosis, and keratomycosis.


Synonyms: *Aspergillus amoenus* Roberg, 1931
- *Aspergillus versicolor var. fulvus* Nakaz. et al., 1932
- *Sterigmatocystis versicolor* Vuill., 1903

**Morphology**

Colonies on CYA 16-25 mm diam, plane or lightly sulcate, low to moderately deep, dense; mycelium white to buff or orange; conidial heads sparse to quite densely packed, greyish green; pink to wine red exudate sometimes produced; reverse orange or reddish brown. Colonies on MEA 12-25 mm diam, low, plane, and dense, usually velutinous; mycelium white to buff; conidial heads numerous, radiate, dull or grey green; reverse yellow brown to orange brown. Colonies on G25N 10-18 mm diam, plane or umbonate, dense, of white, buff or yellow mycelium; reverse pale,
yellow brown or orange brown. No growth at 5°C. Usually no growth at 37°C, occasionally colonies up to 10 mm diam formed.

Conidiophores borne from surface or aerial hyphae, stipes 300-600µm long, with heavy yellow walls, vesicles variable, the largest nearly spherical, 12-16µm diam, fertile over the upper half to two-thirds, the smallest scarcely swollen at all and fertile only at the tips, bearing closely packed metulae and phialides, both 5-8µm long; conidia mostly spherical, very small, 2.0-2.5µm diam, with walls finely to distinctly roughened or spinose, borne in radiate heads.

*Aspergillus versicolor* isolates produce the aflatoxin precursor sterigmatocystin, a compound that is mutagenic and tumorigenic. Animal feed infested with three morphotypes of *A. versicolor*, all of which produce sterigmatocystin, have been implicated in dairy animal toxicosis, but it is unknown whether sterigmatocystin caused the toxicosis.

*Aspergillus versicolor* has been implicated as the causitive agent of disseminated aspergillosis in dogs has probably caused aspergillosis in transplant recipients and has been isolated from the infected eye of a patient suffering from HIV.

**A. versicolor, Mycota, Mold-pro.com, fungi myospecies inf.**

[Image: www.tamagawa.ac.jp]
4.7. Aspergillus section Sparsi

- The *Aspergillus sparsus* species group (*Aspergillus* section *Sparsi*; Gams et al. 1985) was established by Raper & Fennell (1965) to accommodate four species isolated from tropical or subtropical soils. Species assigned to this group have large globose conidial heads, which irregularly split with age, with colours ranging from light grey to olive-buff.

- The data obtained by Varga et al. (2010) indicate that the revised section *Sparsi* includes 10 species:

  1. *Aspergillus anthodesmis*,
  2. *Aspergillus biplanus*,
  3. *Aspergillus conjunctus*,
  4. *Aspergillus diversus*,
  5. *Aspergillus funiculosus*,
  6. *Aspergillus implicatus*,
  7. *Aspergillus panamensis*,
  8. *Aspergillus quitensis*,
  9. *Aspergillus sparsus*,
  10. *Aspergillus haitiensis* (recently described)
• Aspergillus quitensis and Aspergillus ecuadorensis are synonyms of Aspergillus amazonicus based on both molecular and physiological data.
• The white-spored species A. implicatus has also been found to belong to this section.
• Aspergillus haitiensis sp. nov. is characterised by whitish colonies becoming reddish brown due to the production of conidial heads, and dark coloured smooth stipes.
• The taxon produces gregatinis, siderin and several unknown but characteristic metabolites.

4.8. Aspergillus Section: Aspergillus (Teleomorph: Eurotium)

• Aspergillus section Aspergillus contains economically important, xerophilic fungi that are widely distributed in nature and the human environment and are known for their ability to grow on substrates with low water activity.
• Eurotium species are the sexual states of Aspergillus species, notably the Aspergillus glaucus group among others. Eurotium is common and is most closely related to Emericella, another genus with Aspergillus anamorphs.
• Health effects, allergenicity, and toxicity of Eurotium are closely related to the Aspergillus anamorph and, for the most part, have not been studied apart from that primary phase. The Aspergillus anamorph is likely to be the identifiable result, at least with primary growth within one week.
• The taxa were revised based on sequence data from four loci, PCR fingerprinting, micro- and macromorphology, and physiology. The number of taxa was reduced to the following species:

1. Aspergillus proliferans (The only anamorphic species)
2. Aspergillus niveoglauclus (≡Eurotium niveoglauclus)
3. Aspergillus brunneus [Eurotium echinulatum].
4. Aspergillus neocarnoyi [Eurotium carnoyi].
5. Aspergillus glaucus [Eurotium herbariorum].
6. Aspergillus repens (Eurotium repens)
7. Aspergillus rubrobrunneus [Eurotium rubrum]
8. Aspergillus tonophilus [Eurotium tonophilus].
9. Aspergillus hollandidicus (Eurotium amstelodami)
10. Aspergillus chevalieri var. intermedius (≡ Eurotium intermedium)
11. Aspergillus equitis (Eurotium chevalieri)
12. Aspergillus cristatus (≡Eurotium cristatum)
13. Aspergillus xerophilus, [Eurotium xerophilum].
4.8.1. *Aspergillus glaucus* Link, 1809

(Teleomorph: *Eurotium herbariorum* (Wiggers) Link, 1809.

*A. glaucus* is not very invasive and is rarely encountered in the clinical laboratory. It has been implicated as a cause of ocular (eye) infections, particularly after some traumatic injury. Cerebral, orofacial, cardiovascular and pulmonary infections are rare but have been reported. *A. glaucus* may also cause sinusitis (nasal) and otitis (ear) infections. *A. glaucus* may be considered an opportunistic fungus particularly with immunocompromised patients.

**Morphology:**

Growth is slow to moderate, maturing in about 7 to 21 days. Colony size expands rather slowly. Colony colouration is media dependent but is described as a dull to deep green to a greyish turquoise, with yellow to orange areas where cleistothecia are being produced. The reverse is pale yellow to yellow. Hyphae are septate and hyaline. **Teleomorph** – Sexual state is seen with the production of cleistothecia (ascomata). These structures are globose to subglobose, about 60 µm to 150 µm in diameter. In their natural state they appear yellow to golden in colour and their presence may be seen macroscopically as distinctly yellowish areas within the maturing colony. Within the cleistothecia/ascomata, 8-celled asci are produced which are released at maturity or when ruptured. The 8-celled asci (10 µm - 12µm diameter) are dehiscent (dissolve) and release individual ascospores on maturity). The Ascospores themselves mature in about two weeks’ time and are lenticular (lens shaped) with a noticeable longitudinal furrow. They range between 5 µm to 7 µm by 3 µm to 5 µm in size.

*Eurotium herbariorum*, B.Flannigan, R Samson & JD Miller

**Anamorph** – smooth walled conidiophores extend between 300 µm – 700 µm in length and are between 7 µm – 12 µm in width. Vesicles are globose (spherical) to subglobose (subspherical) to pyriform (tear-drop) in shape and roughly 18-30 µm in diameter. *A. glaucus* is uniseriate with phialides 7 – 11 µm to 3 – 7 µm in size and generally covers most of the vesicle. The conidia (4 µm to 8 µm diameter) are spherical to ellipsoidal in shape and are echinulate to spinose (finely roughened/fine sp
4.8.2. *Aspergillus equitis* Samson & Gams, 1985


**Morphology**

Colony diameters on Czapek’s Agar 2.8-3.2 cm in 14 days at 25°C; conidial heads radiate, deep greenish glaucous to pistachio green; mycelium yellow. Cleistothecia yellow to buffy citrine, or deep colonial buff to olive; soluble pigment yellow; exudate clear; reverse yellow to Saccardo’s umber. Colony diameters on Czapek’s Agar with 20% added sucrose 6.0-6.5 cm in 14 days at 25°C; conidial heads radiate, gnaphalium green to near dark sage green; mycelium yellow to greyish yellow orange shades; exudate clear; reverse near asphodel green to apricot yellow, or mahogany red to bay; stipes 62-680 × 7.0-20.0 μm, smooth, colorless to pale brown; vesicles obovoid to globose 10.0-46.0 μm wide. Aspergilla uniseriate, phialides covering the entire surface of the vesicle, 4.0-13.1 × 2.8-6.2 μm. Conidia ellipsoidal to doliiform, less commonly subglobose, rough to irregularly roughened, 3.2-7.1 × 2.4-5.0 μm. Cleistothecia greyish yellow, subglobose to globose, up to 178 μm wide, asci 8-spored, spherical to subspherical, ascospores lenticular, with wall smooth to finely roughened, with 2 distinct longitudinal trough flanges, 4.2-5.4 × 3.3-4.0 μm. Colony diameters on M40Y 7.5-8.5 cm in 14 days at 25°C; conidial heads abundant, light hellebore green. Cleistothecia abundant as on C20S enmeshed in orange-red hyphae; reverse orange-brown.


Colony diameters on Czapek’s Agar 2.0-2.5 cm in 14 days at 25°C; conidial heads radiate to columnar, dark terre verte to dusky green; mycelium white to yellow; reverse uncolored, amber yellow to olive lake; cleistothecia yellow. Colony diameters on Malt Extract Agar 1.8-2.2 cm in 14 days at 25°C; conidial heads radiate, dark grass green to ivy green; mycelium white to yellow; reverse colorless or dull wax yellow to dull primuline yellow; cleistothecia yellow. Colony diameters on Czapek’s Agar with 20% added sucrose 3.5-4.5 cm in 14 days at 25°C; conidial heads radiate to columnar, ivy green to dark grass green; mycelium white to yellow; reverse uncolored, yellow to pale green brown; stipes 60-360 × 4.0-16.0 μm, smooth, colorless, or pale brown to middle brown; vesicles globose or subglobose to ovoid or pyriform, 6.8-32.5 μm in diameter. *Aspergilla* uniseriate, phialides covering 1/2 to 4/5 of the vesicle, 3.2-9.3 × 3.0-5.3 μm. Conidia globose or subglobose to ovoid, 3.3-6.4 × 3.0-5.2 μm, rough to irregularly roughened. Cleistothecia globose to subglobose, yellow 60.0-168.0 μm in diameter. Asci 8-spored, subglobose to globose, 8.7-12.7 × 8.0-10.3 μm. Ascospores lenticular 3.8-5.2 × 3.3-4.8 μm, longitudinal furrow with two irregular ridges, convex surfaces irregularly roughened.
4.9. *Aspergillus section Terrei* (Teleomorph:Fennellia)

*Aspergillus* section *Terrei* (Gams *et al.* 1985; *A. terreus* species group according to Raper & Fennell 1965) includes species with columnar conidial heads in shades of buff to brown. The most important species of this section is *A. terreus*, which is an ubiquitous fungus in our environment. Strains of this cosmopolitan species are frequently isolated from desert and grassland soils and compost heaps, and as contaminants of plant products like stored corn, barley and peanuts.

Molecular studies have since indicated that this section should be expanded to include the following species (Peterson 2000, 2008, Varga *et al.* 2005):

1. *Aspergillus terreus*
2. *A. terreus* var. *africanus*
3. *A. terreus* var. *aureus*
4. *Aspergillus niveus*
5. *Aspergillus carneus*,
6. *Aspergillus niveus* var. *indicus*,
7. *Aspergillus allahabadii*,
8. *Aspergillus ambiguus*
9. *Aspergillus microcysticus*
Aspergillus terreus is an economically important species from a number of aspects. *Aspergillus terreus* isolates are used in the fermentation industry for the production of itaconic acid and itatartaric acid and for enzyme production.

- *Aspergillus terreus* isolates produce a range of secondary metabolites, some of which have properties valuable for mankind, including lovastatin, a cholesterol lowering drug, the antitumor metabolites terrein, quadrone and asterriquinone, acetylcholinesterase inhibitors like territrem B and terreulactone, butyrolactones, and cyclosporine A.
- Antiviral compounds such as acetylaranotin has also been reported from *Aspergillus terreus*.
- Other secondary metabolites reported to be produced by *A. terreus* isolates are considered as mycotoxins, including citreoviridin, patulin, citrinin, terretin, geodin, territrems, gliotoxin, and cytochalasin E.
- *Aspergillus terreus* is also an important human pathogen, and often causes disseminated infection with increased lethality compared to other *Aspergillus* spp.

4.9.1. *Aspergillus terreus* Thom, (1918)

Synonym: *Aspergillus terrestris*

**Morphology** ([http://www.bcrc.firdi.org.tw/fungi/fungal](http://www.bcrc.firdi.org.tw/fungi/fungal))

Colonies on potato dextrose agar at 25°C are beige to buff to cinnamon. Reverse is yellow and yellow soluble pigments are frequently present. Moderate to rapid growth rate. Colonies become finely granular with conidial production. Hyphae are septate and hyaline. Conidial heads are biseriate (containing metula that support phialides) and columnar (conidia form in long columns from the upper portion of the vesicle). Conidiophores are smooth-walled and hyaline, 70 to 300µm long, terminating in mostly globose vesicles. Conidia are small (2-2.5 µm), globose, and smooth. Globose, sessile, hyaline accessory conidia (2-6 µm) frequently produced on submerged hyphae.

On Malt-Agar growth medium (MA) (initial pH 5) – Moderately fast growing colonies (reaching 78 cm in 21 days), velvet-like, white at first and then becoming cinnamon to brown-orange. The reverse is cream to slightly orangey. Emission of a yellowish pigment in the medium. The species slightly acidifies the medium (final pH 4).

This fungus is readily distinguished from the other species of *Aspergillus* by its cinnamon-brown colony colouration and its production of aleurioconidia. *Aspergillus terreus* is a thermotolerant species since it has optimal growth in temperatures between 35–40 °C, and maximum growth within 45–48 °C.
4.10. Aspergillus Section Flavipeses (Teleomorph: Fennellia)

*Aspergillus flavipes*
*Aspergillus niveus*
*Aspergillus iizukae*
*Aspergillus carneus*
*Aspergillus aureofulgens*
*Aspergillus janus*
*Aspergillus brevijanus*

4.10.1. *Aspergillus flavipes* (Bain. & Sart.) Thom & Church, 1926.

Colony diameters on Czapek’s Agar 1.3-1.5 cm in 14 days at 25°C, dense, raised; conidial heads radiate to loosely columnar, white to cartridge buff; mycelium white to pale capucine buff; exudate abundant, light yellow; soluble pigment buff-yellow; reverse deep chrome or
capucine orange to amber brown; stipes 140-1510 × 2.8-11.1 μm, colorless or light yellow to pale brown, smooth to slightly roughened; vesicles ovoid, subglobose or pyriform, 6.0-29.4 μm wide. Aspergilla biseriate, metulae covering 1/2 to 4/5 of the vesicle, 4.0-9.4 × 2.5-5.7 μm; phialides 4.8-8.7 × 2.2-3.0 μm. Conidia globose to subglobose, 2.0-4.0 μm in diameter, smooth walled. Colony diameters on Malt Extract Agar 3.0-3.5 cm in 14 days at 25°C, plane to velutinous; conidial heads radiate to columnar, white to light buff; mycelium white to pinkish buff; soluble pigment red brown; reverse light pinkish cinnamon or vinaceous-cinnamon to mikado brown.

Gardner, D. E. flavipes, Wiley & Simmons,

4. 11. Section: Circumdati  (Teleomorph: Neopetromyces)

Aspergillus section Circumdati historically includes species with biseriate conidial heads in shades from yellow to ochre. Species of Aspergillus section Circumdati are economically important as ochratoxin A (OA) producing spoilage organisms. Aspergillus section Circumdati formed two main clades, which could also be distinguished based on phenotypic methods. A sexually reproducing ochratoxin producing species and ochratoxin non-producing. (Frisvad et al., 2004). The section contains the following species:

1. Aspergillus auricomus
2. Aspergillus bridgeri
3. Aspergillus cretensis
4. Aspergillus elegans
5. Aspergillus flocculosus
6. *Aspergillus insulicola*
7. *Aspergillus melleus*
8. *Aspergillus neobridgeri*
9. *Aspergillus ochraceus*
10. *Aspergillus ostianus*
11. *Aspergillus persii*
12. *Aspergillus petrakii*
13. *Aspergillus pseudoelegans*
14. *Aspergillus robustus*
15. *Aspergillus roseoglobulosus*
16. *Aspergillus sclerotiorum*
17. *Aspergillus steynii*
18. *Aspergillus sulphurosus*
19. *Aspergillus westerdijkiae*
20. *Neopetromyces muricatus*

### 4.11.1. *Aspergillus ochraceus* K. Wilh., (1877)

**Synonyms:**
- *Sterigmatocystis ochracea* (G. Wilh.) Tiegh. (1877)
- *Aspergillus alutaceus* Berk. & M.A. Curtis, (1875)
- *Aspergillus ochraceus var. microsporus* Tirab., (1908)
- *Sterigmatocystis japonica* Aoki et al. (1951)

**Morphology:**

Colony diameters on Czapek’s Agar 3.0-3.5 cm in 10 days at 25°C, wrinkled; conidial heads spherical, or splitting into compact divergent columns, cream color, pinkish buff or near dark olive-buff; mycelium white, inconspicuously floccose to floccose; exudate uncolored; reverse dull yellow brown to victoria lake; soluble pigment, pale capucine buff; stipes 360-1390 × 4.0-16.0 μm, pale yellow to light yellow brown, slightly to coarsely roughened; vesicles spherical to subspherical, 8.8-46.0 μm in diameter. Aspergilla biseriate, metulae covering the entire surface of the vesicle, 4.8-33.3 × 2.4-10.3 μm; phialides 5.6-143.0 × 1.8-4.8 μm. Conidia spherical to subspherical, smooth to irregular rough, 2.0-3.8 μm. Sclerotia produced by the same isolate, purple, up 1000 μm in diameter. Colony diameters on Malt Extract Agar 5.0-5.5 cm in 10 days at 25°C, more or less floccose; conidial heads globose or splitting into a few columns, near antimony yellow to ochraceous-buff; mycelium white, reverse dull yellow brown to pale auburn.
4. 12. *Aspergillus* section *Flavi* (Teleomorph: *Petromyces*)

- *Aspergillus* section *Flavi* includes species with conidial heads in shades from yellow-green to brown, and dark sclerotia
- Several species assigned to this section are either important mycotoxin producers including aflatoxins, cyclopiazonic acid, ochratoxins and kojic acid, or are used in oriental food fermentation processes and as hosts for heterologous gene expression.
- The data obtained by Varga *et al.* (2011) using morphological characters, extrolite production and partial calmodulin, β-tubulin and ITS sequences indicated that *Aspergillus* section *Flavi* involves 22 species:
  1. *Aspergillus albertensis*
  2. *Aspergillus alliaceus*
  3. *Aspergillus arachidicola*
  4. *Aspergillus avenaceous*
  5. *Aspergillus bombycis*
  6. *Aspergillus coremiformis*
  7. *Aspergillus caelatus*
  8. *Aspergillus coremiformis*
  9. *Aspergillus flavus*
  10. *Aspergillus lanosus*
  11. *Aspergillus leporis*
  12. *Aspergillus minisclerotium*
  13. *Aspergillus nomius*
  14. *Aspergillus oryzae*
  15. *Aspergillus parasiticus*,

40
16. Aspergillus parvisclerotigenus
17. Aspergillus pseudocaelatus
18. Aspergillus pseudonomius
19. Aspergillus pseudotamarii
20. Aspergillus sojae
21. Aspergillus tamari
22. Aspergillus togoensis

- The A. flavus« clade includes species characterised with Q-10(H2) as their main ubiquinone, conidial colours in shades of green and dark sclerotia.

1. Aspergillus flavus Group I includes isolates producing only aflatoxin B and having large or small sclerotia. This group also includes isolates of A. oryzae, which has previously been described as having a recombining population species of this clade, P. alliaceus and P. albertensis, produce high amounts of OA (50–300 mg/mL), and are considered to be responsible for OA contamination of figs.

2. Aspergillus flavus Group II includes isolates that may produce aflatoxins B or G, and have large or small sclerotia.

3. Aspergillus Group III includes isolates able to produce both aflatoxins B and G and have small sclerotia,

4. Aspergillus flavus is the most common species associated with aflatoxin contamination of agricultural crops.

5. flavus soil populations also contain isolates from two morphologically distinct sclerotial size variants, termed the L-strain for isolates with average sclerotial size greater than 400 μm and the S-strain for isolates with sclerotial size less that 400 μm. On typical laboratory growth media S-strain isolates produce higher levels of aflatoxins, more abundant sclerotia, and generally fewer conidia. Atoxigenic S-strain isolates are very rarely found in natural environments.
4.12.1. *Aspergillus flavus* Link, 1809

**Synonyms:** *Monilia flava* (Link) Pers., (1822)
*Sterigmatocystis lutea* Tiegh., (1877)
*Aspergillus flavus var. proliferans* Anguli, Rajam, Thirum., Rangiah & Ramamurthi, (1965)

**Morphology**

*A. flavus* is known as a velvety, yellow to green or brown mould with a goldish to red-brown reverse. On Czapek dox agar, colonies are granular, flat, often with radial grooves, yellow at first but quickly becoming bright to dark yellow-green with age. Conidial heads are typically radiate, mostly 300-400 um in diameter, later splitting to form loose columns. The conidiophores are variable in length, rough, pitted and spiny. They may be either uniseriate or biseriate. They cover the entire vesicle, and phialides point out in all directions. Conidia are globose to subglobose, conspicuously echinulate, varying from 3.5 to 4.5 mm in diameter. Based on the characteristics of the sclerotia produced, *A. flavus* isolates can be divided into two phenotypic types. The S strain produces numerous small sclerotia (average diameter ,400 mm). The L strain produces fewer, larger sclerotia (Cotty, 1989). Within the S strain, some isolates, termed SB, produce only B aflatoxins, whilst others, named SBG, produce both B and G aflatoxins.

*Aspergillus flavus*: human pathogen, allergen and mycotoxin producer
4.12.2. *Aspergillus parasiticus* Speare, 1912  
Synonyms: *Aspergillus flavus* subsp. *parasiticus* (Speare) Kurtzman, Smiley, Robnett & Wicklow, 1986  
*Aspergillus chungii* Y.K. Shih, (1936)

**Morphology**
Colony diameters on Czapek’s Agar larger than 9 cm in 10 days at 25°C, distinctly floccose, sporulation abundant at margin; mycelium fimbriate, white; reverse uncolored; conidial heads mostly radiate or splitting into fine columns or rarely globose, small, primuline yellow, or wax yellow to yellowish citrines; stipes smooth to roughened, colorless, 86-2140 × 6.8-24.0 μm; vesicles globose to pyriform, 19.0-94.0 μm wide. Aspergilla mostly biseriate, occasionally uniseriate; metulae covering 1/2 to the whole surface of the vesicle, 9.5-21.4 × 4.8-12.7 μm; phialides 8.3-15.1 × 3.8-6.0 μm; conidia globose to subglobose, 5.5-8.3 × 4.4-7.1 μm, irregularly roughened to very roughened. Colony diameters on Malt Extract Agar 6.5-7.0 cm in 10 days at 25°C, floccose to plane; mycelium white; conidial heads distinctly radiate, occasionally loosely columnar, yellowish oil green, serpentine green to grass green, or cedar green; reverse colorless;
4.12.3. *Aspergillus oryzae* (Ahlb.) Cohn, 1884

Synonyms: *Eurotium oryzae* Ahlb., 1878

*Aspergillus flavus var. oryzae* (Ahlb.) Kurtzman, M.J. Smiley, Robnett & Wicklow1986

**Morphology**

Colony diameters on Czapek’s Agar 4.5-5.5 cm in 10 days at 25°C, floccose; conidial heads radiate, or splitting into several loose columns, Kronberg’s green to citron green; mycelium white; reverse cream color to mustard yellow and pale isabella color; soluble pigment light yellow; stipes smooth to rough, hyaline, 56-1160 × 6.4-20.6 μm; vesicles globose, subglobose, pyriform to somewhat elongate, 15.8-50.0 μm wide. Aspergilla uniseriate, biseriate, or both coexisting on the same vesicle, metulae covering the entire vesicle, 5.2-36.5 × 2.8-9.5 μm; phialides 4.0-14.3 × 2.8-7.1 μm, hyaline to light yellow; phialides of uniseriate aspergilla covering 1/2 to the entire surface of the vesicle. Conidia subglobose, rarely ellipsoidal or ovoid, 2.8-6.0 μm wide, with walls smooth to irregularly roughened. Colony diameters on Malt Extract Agar larger than 9 cm, floccose, in 10 days at 25°C; co-nidial heads enmeshed within the loosely aerial mycelium, ivy green to citron green, and olive-ocher to olive-yellow; mycelium white; reverse uncolored to pale buffy olive in center.
4.13. Aspergillus Section: Cremei (Teleomorph: Chaetosartorya)

1. *Aspergillus stromatoides*
2. *Aspergillus stromatoides*
3. *A. itaconicus*
4. *Aspergillus cremea*
5. *Aspergillus chrysella,*
6. *Aspergillus wentii,*
7. *Aspergillus dimorphicus,*
8. *Aspergillus pulvinus*
10. *Aspergillus gorakhopureensis*
11. *Aspergillus bruneouniseriatis*

Synonyms: *Aspergillus archaeoflavus* Blochwitz, (1933)
*Aspergillus wentii* var. *minimus* Nakaz. et al., (1934)


This section involves the anamorphs of at least 20 sexual *Neosartorya* species, and 5 asexual aspergilli. The most important species among them is *Aspergillus fumigatus*, which is an ubiquitous filamentous fungus in the environment, and also an important human pathogen. Several *Neosartorya* species have also been described as causative agents of human diseases including invasive aspergillosis, osteomyelitis, endocarditis and mycotic keratitis. Many of the *Neosartorya* species produce several mycotoxins, many of which may cause serious health hazards.

**Synonyms:**
- *Aspergillus fumigatus* var. *cellulosae* Sartory, Sartory & Mey. (1935)
- *Aspergillus fumigatus* var. *coeruleus* Malchevsk. (1939)
- *Aspergillus fumigatus* var. *ellipticus* Raper & Fennell (1965)
- *Aspergillus fumigatus* var. *fumigatus* Fresen. (1863)
- *Aspergillus fumigatus* var. *helvolus* Yuill (1937)
- *Aspergillus fumigatus* var. *lunzinense* Svilv. (1941)
- *Aspergillus fumigatus* var. *minimus* Sartory (1919)
- *Aspergillus phialoseptus* Kwon-Chung (1975)
- *Aspergillus bronchialis* Blumentritt (1901)
- *Aspergillus septatus* Sartory & Sartory (1943)

**Description**

Colony diam (7 d): CYA25: 21-67 mm; MEA25: 25-69 mm; YES25: 48-74 mm; OA25: 34-62 mm, CYA37: 60-75 mm, CREA: poor growth, no or very weak acid production.

Colour: greyish turquoise or dark turquoise to dark green to dull green. Reverse colour (CYA): creamy, yellow to orange.

4.14.2. *Aspergillus felis*

Colonies grow rapidly on CYA agar attaining a diameter of 5.0 to 5.5 cm in 7 days at 25°C and on MEA reach 5.5 cm in diameter in 7 days at 25°C. On CYA the colony texture is mostly floccose; colonies are usually white and often sporulate poorly. On MEA colonies are more or less velvety with abundant greenish sporulation occurring after 5 to 7 days. In reverse, colonies are cream to light green. Conidiophores are uniseriate with greenish stipes and subclavate, “nodding” heads. Vesicles are subclavate with a diameter of 15–16.5 µm. Conidia are green, globose to subglobose, finely roughened and 1.5–2.5 µm in dimensions. Cleistothecia are white to creamish, 100–230 µm. Asci are globose, 8-spored, 12–16 µm in diameter. Ascospores are lenticular with two prominent equatorial crests and with short echinulate convex surfaces 5.0–7.0×3.5–5.0 µm.

This species had been found in cats with chronic invasive FRS and retrobulbar masses (SOA), IPA or with sinonasal cavity infection only (sinonasal aspergillosis, SNA), in a dog with disseminated IA, in a human with chronic IPA and in an indoor air sample in Germany.

Fungi like *Aspergillus felis* can be easily misidentified as the closely related fungus *Aspergillus fumigatus*. However, *Aspergillus felis* is intrinsically more resistant to antifungal drugs than *Aspergillus fumigatus* and this has important implications for therapy and prognosis.
4. 15. Aspergillus Section: Clavati  
(Teleomorph: Neocarpenteles)

Aspergillus section Clavati has been revised by Varga et al. (2007) using morphology, secondary metabolites, physiological characters and DNA sequences. Phylogenetic analysis of beta-tubulin, ITS and calmodulin sequence data indicated that Aspergillus section Clavati includes 6 species:

1. Aspergillus clavatus
2. giganteus
3. longavesica
4. clavatonanicus
5. rhizopodus
6. Neocarpenteles acanthosporus

4. 15. 1. Aspergillus clavatus Desmazières (1834)

A. pallidus Kamyschko, 1963

Colony diameters on Czapek’s Agar 4.7-5.0 cm in 14 days at 25°C, zonation conspicuous to inconspicuous; conidial heads radiate or splitting into well defined columns in age, niagara green to bice green, or artemisia green to slate-olive (R., Plate XVII, XXXIII, XLVII); mycelium white; exudate clear; reverse colorless, or ivory yellow to cartridge buff (R., Plate XXX); stipes 250-2300 × 4.8-40.0 μm, uncolored, smooth; vesicles clavate, 8.7-80.0 μm wide. Aspergilla uniseriate, phialides covering the entire surface of the vesicle, 5.3-21.4 × 2.4-5.6 μm. Conidia subspherical, ellipsoidal, occasionally cylindrical, 3.3-7.1 × 2.4-4.4 μm, smooth. Colony diameters on Malt Extract Agar 5.0-5.5 cm in 14 days at 25°C, zonation conspicuous; conidial heads radiate or splitting into well defined columns, bluish gray-green to artemisia green (R., Plate XLII, XLVII); mycelium white; reverse uncolored.
4.16. Aspergillus Section:Nidulantes (Teleomorph: Emericella)

1. A. nidulans
2. A. quadrilineata
3. E. rugulosa
4. E. nidulans var. echinulata

4.16.1. Aspergillus nidulans (Eidam) G. Winter (1884)
Teleomorphic state: Emericella nidulans
Synonyms: Sterigmatocystis nidulans Eidam (1883)
Diplostephanus nidulans (Eidam) Neveu-Lem. (1921)
Sterigmatocystis nidulans var. nicollei Pinoy. (1906)
Aspergillus nidulans var. cesarii Pinoy (1915)
Morphology
Colonies on potato dextrose agar at 25°C are dark green with orange to yellow in areas of cleistothecial production. Reverse is purplish to olive. Exudate is usually present and may be brown to purplish. Growth rate is slow to moderate in comparison with other clinically significant Aspergillus species.

Hyphae are septate and hyaline. Conidial heads are columnar. Conidiophores are brown, short (60-150 µm in length), and smooth-walled. Vesicles are hemispherical, small (8-12 µm in diameter), with metulae and phialides occurring on the upper portion. Conidia are globose (3-4 µm) and rough. A. nidulans is a homothallic species capable of producing the teleomorph (sexual stage) without mating studies. The ascomycetous telemorph (Emericella nidulans) produces brown to black globose cleistothecia (100-250 µm) that are engulfed with globose Hülle cells. Ascospores are reddish brown, lenticular (4 x 5 µm), with two longitudinal crests.
4.17. Aspergillus Section: Ornati  (Teleomorph: Hemicarpenteles)

4.17.1. Aspergillus ornatus Raper, Fennell & Tresner (1953)
Synonyms: Sclerocleista ornata (Raper, Fennell & Tresner) Subram., (1972)
Neosartorya ornata (Raper, Fennell & Tresner) Malloch & Cain, (1973)
Hemicarpenteles ornatus (Raper, Fennell & Tresner) Arx, (1974)
Hemicarpenteles ornata (Subram.) Arx (1974)
Chaetosartorya ornata (Raper, Fennell & Tresner) Bilai & Koval, (1988)

4.18. Aspergillus sect. Aeni
Aspergillus sect. Aeni is a new section that includes the following species
1. Aspergillus karnatakaensis
2. Aspergillus aeneus,
3. Aspergillus crustosus,
4. Aspergillus eburneocrementeus,
5. Aspergillus heyangensis,
6. Emericella bicolor,
7. Emericella discophora,
8. Emericella spectabilis,
9. E. foeniculicola.

Aspergillus karnatakaensis isolates were found to produce karnatakafurans A and B, terrein, gregatins, asteltoxin and the partially characterised metabolite NIDU. Both gregatins and NIDU are also produced by A. granulosus, while karnatakafurans are produced in common with A. aeneus and A. multicolor. Emericella bicolor produces sterigmatocystin, versicolorins, some anthraquinones, and a polar extrolite with end-absorptio; E. foeniculicola produces sterigmatocystin (and many other sterigmatocystin and versicolorin-related compounds), xanthocillin derivatives, and the partially characterized (but common) metabolite DRI; E. spectabilis produces two members of the shamixanthone biosynthetic family (both more polar than shamixanthone itself) and a member of the sterigmatocystin biosynthetic family; A. heyangensis produces a decaturin in common with A. aeneus and A. karnatakaensis and NIDU, while E. discophora produces sterigmatocystin and versicolorins (Varga et al., 2010).
4.18.1. *Aspergillus granulosus* Raper and Thom (1944)

**Morphology**

Colonies are cream to white and floccose at the periphery and buff to yellowish tan centrally, with a very slight clear exudate. Colonies on CZA are mostly cream, more irregularly furrowed, and exhibited reduced conidiation. The central granular areas on PFA consisted of colorless masses of thick-walled (6 to 8 μm), predominately globose but also oval to elongate to irregularly shaped Hülle cells with individual, mature cells ranging from 20 to 40 μm. Robust *Aspergillus* fruiting heads are sparse and are borne on long (200 to 480 μm), subhyaline to brown, smooth, thick-walled conidiophores terminating in small (12 to 18 μm wide by 15 to 25 μm long), oval to elliptical vesicles. Metulae and bottle-shaped phialides of almost equal length (3.5 to 5.5 μm) covered most of the surface of the vesicle. Conidia pale green in mass, globose, and finely echinulate, measuring 3.5 to 5.5 μm in diameter. More commonly, fruiting structures are reduced in size with small, *Penicillium*-like vesicles or single chains of conidia are borne from solitary phialides.
5. Aspergillosis in man

5.1. Pulmonary aspergillosis

5.1.1. Aspergilloma (Saprophytic aspergillosis, fungus ball)

- Aspergilloma is an *Aspergillus* infection without tissue invasion.
- The aspergilloma is a mass composed of fungal hyphae, inflammatory cells, fibrin, mucus and tissue debris that develops in a pre-existing cavity in the lung, without invade the surrounding lung parenchyma or blood vessels.
- The most common underlying causes are tuberculosis and sarcoidosis. Other conditions that occasionally may be associated with aspergilloma include bronchogenic cyst, pulmonary sequestration, and pneumatoceles secondary to *Pneumocystis carinii* pneumonia in patients with acquired immunodeficiency syndrome (AIDS).
- At radiography, aspergilloma is characterized by the presence of a solid, round or oval mass with soft-tissue opacity within a lung cavity. Typically, the mass is separated from the wall of the cavity by an airspace of variable size and shape, resulting in the “air crescent” sign. A change in the position of the fungus ball after moving the patient, demonstrating that this mass is mobile because does not usually invade the surrounding lung parenchyma.
- Aspergillomas are often associated with thickening of the cavity wall and adjacent pleura. In such cases, pleural thickening may be the earliest radiographic sign before any visible changes are seen within the cavity. Approximately 10% of mycetomas resolve spontaneously. Reversibility of the pleural thickening corresponding to the resolution of intracavitary fungal material has been demonstrated at follow-up radiography.
- Surgical resection of the cavity and removal of the fungus ball is usually indicated in patients with recurrent haemoptysis, if their pulmonary function is sufficient to allow surgery or bronchial artery embolization in patients with poor lung function.
Aspergilloma - "Chest x-ray of a man with extensive bullous lung

pathologyimages.wordpress.com, de.wikipedia.org Aspergilloma,

www.histopathology-india.net www.flickr.com
Recently reported cases:
1. Aspergilloma and massive haemoptysis. \textsuperscript{45}
2. A rare case of calcified pulmonary aspergilloma\textsuperscript{46}.
3. Adjuvant antifungal therapy after pulmonary surgery for aspergilloma: is it useful? \textsuperscript{47}
4. Aspergilloma and the surgeon. \textsuperscript{48}
5. Pulmonary Diseases with Imaging Findings Mimicking Aspergilloma. Lung. \textsuperscript{49}
6. Is video-assisted thoracic surgery a versatile treatment for both simple and complex pulmonary aspergilloma? \textsuperscript{50}
7. Pulmonary Aspergilloma: An Unexpected Complication of Radiofrequency Ablation in the Management of Targeted Therapy for a Patient With Metastatic Renal Cell Carcinoma. \textsuperscript{51}
8. Treatment of pulmonary aspergilloma in Srinagarind Hospital\textsuperscript{52}.
9. Surgical therapy of pulmonary aspergillomas: a 30-year North American experience. \textsuperscript{53}
10. Intrapulmonary aspergilloma in an old tuberculous cavity with access to the bronchial system. \textsuperscript{54}
11. Case 3: aspergilloma. \textsuperscript{55}
12. Pulmonary aspergilloma: a treatment challenge in sub-Saharan Africa. \textsuperscript{56}
13. [Gougerot-Sjögren syndrome complicated by pulmonary aspergilloma]. \textsuperscript{57}
14. A case of pulmonary aspergilloma treated with radiofrequency ablation. \textsuperscript{58}
15. [Surgical treatment of pulmonary tuberculosis complicated with aspergilloma]. \textsuperscript{59}
16. Always expect the unexpected: lung abscess due to pseudomonas aeruginosa mimicking pulmonary aspergilloma in acute B-cell leukemia. \textsuperscript{60}
17. Video-assisted thoracic surgery for pulmonary aspergilloma: a safe and effective procedure. \textsuperscript{61}
18. 'Monod' and 'air crescent' sign in aspergilloma. \textsuperscript{62}
19. Calcium oxalate crystal deposition in a patient with Aspergilloma due to Aspergillus niger. \textsuperscript{63}
20. Surgical treatment of aspergilloma grafted in hydatid cyst cavity. \textsuperscript{64}
21. Haemoptysis after four years of lobectomy for aspergilloma. \textsuperscript{65}
22. Aspergilloma coexisting with idiopathic pulmonary fibrosis: a rare occurrence. \textsuperscript{66}
23. Aspergilloma mimicking a lung cancer. \textsuperscript{67}
24. A Case of Endobronchial Aspergilloma Associated with Foreign Body in Immunocompetent Patient without Underlying Lung Disease. \textsuperscript{68}
25. Pulmonary aspergilloma in a cavity formed after percutaneous radiofrequency ablation. \textsuperscript{69}
26. Co-existence of HIV, active tuberculosis and aspergilloma in a single individual--a case report. \textsuperscript{70}
5.1.2. Allergic bronchopulmonary aspergillosis (Hypersensitivity reaction)

- Allergic bronchopulmonary aspergillosis (ABPA) is seen most commonly in patients with long-standing bronchial asthma.
- It is characterized by the presence of plugs of inspissated mucus containing *Aspergillus* organisms and eosinophils.
- This results in bronchial dilatation typically involving the segmental and subsegmental bronchi.
- It is caused by a complex hypersensitivity reaction to *Aspergillus* organisms.
  - The fungi proliferate in the airway lumen, resulting in the production of a constant supply of antigen.
  - A type I hypersensitivity reaction with immunoglobin E and immunoglobin G release occurs.
  - Immune complexes and inflammatory cells are then deposited in the bronchial mucosa, producing necrosis and eosinophilic infiltrates (type III reaction) with bronchial wall damage and bronchiectasis.
  - Excessive mucus production and abnormal ciliary function lead to mucoid impaction.
- Many patients cough up thick mucous plugs in which hyphal fragments can be demonstrated at culture or histologic analysis.
- Acute clinical symptoms include recurrent wheezing, malaise with low-grade fever, cough, sputum production, and chest pain. Patients with chronic allergic bronchopulmonary aspergillosis may also have a history of recurrent pneumonia.
- Radiologic manifestations include homogeneous, tubular, finger-in-glove areas of increased opacity in a bronchial distribution, usually predominantly or exclusively involving the upper lobes. Occasionally, isolated lobar or segmental atelectasis may occur. CT findings in allergic bronchopulmonary aspergillosis consist primarily of mucoid impaction and bronchiectasis involving predominantly the segmental and subsegmental bronchi of the upper lobes. In approximately 30% of patients, the impacted mucus has high attenuation or demonstrates frank calcification at CT.
Areas of tubular (Panel A, arrows) and cystic (Panel A, arrowhead) bronchiectasis, predominantly in the upper lobes, and bilateral mucous plugging (Panel B, arrows).

The CXR shows bronchial wall thickening and impressive central bronchiectasis.

Recently reported cases
1. Antifungal treatment in allergic bronchopulmonary aspergillosis with and without cystic fibrosis: a systematic review. Clin Exp Allergy. 71
2. Omalizumab therapy for allergic bronchopulmonary aspergillosis in children with cystic fibrosis: a synthesis of published evidence.72
3. Fungal allergy in asthma-state of the art and research needs.73
4. Excellent outcome of Aspergillous endophthalmitis in a case of allergic bronchopulmonary aspergillosis.74
5. A retrospective study of patients with a delayed diagnosis of allergic bronchopulmonary aspergillosis/allergic bronchopulmonary mycosis.75
6. Allergic bronchopulmonary aspergillosis coexists with hereditary bisalbuminemia.76
7. Role of inhaled amphotericin in allergic bronchopulmonary aspergillosis.77
8. Pulse methylprednisolone in allergic bronchopulmonary aspergillosis exacerbations.78
9. Unexpected decrease in total IgE in a patient with allergic bronchopulmonary aspergillosis treated with omalizumab.79
12. [Allergic bronchopulmonary aspergillosis in patients with chronic obstructive pulmonary disease: report of 3 cases]. 
13. Evaluation of serum levels of carcinoembryonic antigen in allergic bronchopulmonary aspergillosis. 
15. Treatment options in severe fungal asthma and allergic bronchopulmonary aspergillosis. 
16. Anti-IgE therapy for allergic bronchopulmonary aspergillosis. 
17. [Analysis of clinical features and allergic status of asthmatic patients with positive serum mycosis-specific IgE]. 
19. Bronchial asthma with ABPA presenting as PTE. 
20. Anti-IgE therapy for allergic bronchopulmonary aspergillosis in people with cystic fibrosis. 
21. Development of allergic bronchopulmonary aspergillosis with central bronchiectasis over a 10-year period: the need to recheck allergen sensitization. 
22. Dissociation between sensitizing and colonizing fungi in patients with allergic bronchopulmonary aspergillosis. 
23. Allergic bronchopulmonary aspergillosis in garden waste (compost) collectors--occupational implications. 
25. Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. ABPA complicating asthma ISHAM working group. 
26. Uncertain areas in the diagnosis of allergic bronchopulmonary aspergillosis in patients with asthma. 
27. When to suspect and work up allergic bronchopulmonary aspergillosis. 
29. Allergic bronchopulmonary aspergillosis presenting as chronic cough in an elderly woman without previously documented asthma. 
30. Coexistence of allergic bronchopulmonary aspergillosis and allergic aspergillus sinusitis in a patient without clinical asthma. 

59
5.1.3. Chronic necrotizing aspergillosis (Semi-invasive aspergillosis)

- Semi-invasive aspergillosis, also known as chronic necrotizing aspergillosis, is an indolent, destructive process of the lung due to local invasion by *Aspergillus* species, with tissue necrosis and granulomatous inflammation.
- Factors associated with the development of this form of aspergillosis include chronic debilitating illness, diabetes mellitus, malnutrition, alcoholism, advanced age, prolonged corticosteroid therapy, and chronic obstructive pulmonary disease.
- Clinical symptoms include chronic cough, sputum production, fever, and constitutional symptoms. In patients with chronic obstructive pulmonary disease, semi-invasive aspergillosis may manifest with a variety of nonspecific clinical symptoms such as cough, sputum production, and fever lasting more than 6 months. Hemoptysis has been reported in 15% of affected patients.
- Radiologic manifestations of semi-invasive aspergillosis include unilateral or bilateral segmental areas of consolidation with or without cavitation or adjacent pleural thickening, and multiple nodular areas of increased opacity. *Aspergillus* necrotizing bronchitis may be seen at CT as an endobronchial mass, obstructive pneumonitis or collapse, or a hilar mass. Only a few reports have described CT findings in *Aspergillus* necrotizing bronchitis involving the central airways; reported abnormalities include circumferential bronchial wall thickening and bronchial obstruction.
- In clinical practice, the diagnosis of *Aspergillus* necrotizing bronchitis is usually based on the presence of abnormal findings at chest radiography and bronchoscopic biopsy, which are consistent with tissue invasion.
Recently reported cases:

1. Chronic necrotizing pulmonary aspergillosis in a renal transplant recipient.\textsuperscript{122}
2. Prognostic factors in 194 patients with chronic necrotizing pulmonary aspergillosis.\textsuperscript{123}
3. [Three autopsy cases of chronic necrotizing pulmonary aspergillosis].\textsuperscript{124}
4. Systemic dissemination of chronic necrotizing pulmonary aspergillosis in an elderly woman without comorbidity: a case report.\textsuperscript{125}
5. Systemic biomarkers of inflammation and haemostasis in patients with chronic necrotizing pulmonary aspergillosis.\textsuperscript{126}
6. Efficacy and safety of short- and long-term treatment of itraconazole on chronic necrotizing pulmonary aspergillosis in multicenter study.\textsuperscript{127}
7. [Chronic necrotizing pulmonary aspergillosis following an infection by Mycobacterium malmoense].\textsuperscript{128}
8. [Retrospective analysis of the safety of four hours administration of liposomal amphotericin B in patients with chronic necrotizing pulmonary aspergillosis].\textsuperscript{129}
9. A surgically treated case of chronic necrotizing aspergillosis with pleural invasion.\textsuperscript{130}
10. Chronic necrotizing pulmonary aspergillosis presenting as bilateral pleural effusion: a case report.\textsuperscript{131}
11. Chronic necrotizing pulmonary aspergillosis.\textsuperscript{132}
12. Resolution of galactomannan antigenemia in a patient receiving oral voriconazole for chronic necrotizing pulmonary aspergillosis.\textsuperscript{133}
13. [Chronic necrotizing pulmonary aspergillosis as a complication of silicosis].\textsuperscript{134}
14. [Case of chronic necrotizing pulmonary aspergillosis complicated by elevated eosinophils and serum IgE].\textsuperscript{135}
15. Chronic necrotizing pulmonary aspergillosis in a patient treated with a tumor necrosis factor-alpha inhibitor.\textsuperscript{136}
16. [Lethal case of chronic necrotizing pulmonary aspergillosis (CNPA)].\textsuperscript{137}
17. Progressive increase in cavitation with the evolution of fungus ball: A clue to the diagnosis of chronic necrotizing pulmonary aspergillosis.\textsuperscript{138}
18. [A case of pulmonary actinomycosis mimicking chronic necrotizing pulmonary aspergillosis].\textsuperscript{139}
19. Clinical characteristics and treatment outcomes of chronic necrotizing pulmonary aspergillosis: a review of 43 cases.\textsuperscript{140}
20. Chronic necrotizing pulmonary aspergillosis or invasive pulmonary aspergillosis.\textsuperscript{141}
5.1.4. Invasive pulmonary aspergillosis

- Invasive pulmonary aspergillosis occurs almost exclusively in immunocompromised patients with severe neutropenia.
- The reasons of the substantial increase in the number of patients at risk for developing invasive aspergillosis include the development of new intensive chemotherapy regimens for solid tumors, difficult-to-treat lymphoma, myeloma, and resistant leukemia as well as an increase in the number of solid organ transplantations and increased use of immunosuppressive regimens for other autoimmune diseases.
- Invasive pulmonary aspergillosis is characterized by the presence of Aspergillus organisms deep to basement membrane of bronchi or bronchioles, usually with a neutrophil reaction and presence of hyphae in the involved airway. Surrounding the airway is often found a variably sized zone of hemorrhage and/or organizing pneumonia.
- Invasive pulmonary aspergillosis is characterized at histologic analysis by the invasion and occlusion of small to medium-sized pulmonary arteries by fungal hyphae, which leads to the formation of necrotic hemorrhagic nodules or pleura-based, wedge-shaped.
- Characteristic CT findings consist of nodules surrounded by a halo of ground-glass attenuation ("halo sign") or pleura-based, wedge-shaped areas of consolidation. These findings correspond to hemorrhagic infarcts. In severely neutropenic patients, the halo sign is highly suggestive of invasive pulmonary aspergillosis.
Acute airway invasive aspergillosis, manifested as a bronchopneumonia. posterng.netkey.at. HRCT.

**Recently reported cases:**

3. Evaluation of galactomannan enzyme immunoassay and quantitative real-time PCR for the diagnosis of invasive pulmonary aspergillosis in a rat model.  
4. Independent contribution of bronchoalveolar lavage and serum galactomannan in the diagnosis of invasive pulmonary aspergillosis.  
5. A neonatal case of chronic granulomatous disease, initially presented with invasive pulmonary aspergillosis.  
6. Host biomarkers of invasive pulmonary aspergillosis to monitor therapeutic response.  
8. What's new in invasive pulmonary aspergillosis in the critically ill.  
9. Galactomannan antigen assay from bronchoalveolar lavage fluid in diagnosis of invasive pulmonary aspergillosis in intensive care units patients.  
10. Invasive pulmonary aspergillosis post extracorporeal membrane oxygenation support and literature review.  
11. Screening of the central nervous system in children withinvasive pulmonary aspergillosis.  
12. Intrapulmonary posaconazole penetration at the infection site in an immunosuppressed murine model of invasive pulmonary aspergillosis receiving oral prophylactic regimens.
15. Invasive pulmonary aspergillosis after influenza a infection in an immunocompetent patient.  
16. Clinical findings in 19 cases of invasive pulmonary aspergillosis with liver cirrhosis.  
17. Altered CD8(+) T-cell counts as an early predictor of prognosis in critically ill immunocompromised patients with invasive pulmonary aspergillosis.  
18. Prognostic value of serum galactomannan index in critically ill patients with chronic obstructive pulmonary disease at risk of invasive pulmonary aspergillosis.  
20. Hypothermic endpoint for an intranasal invasive pulmonary aspergillosis mouse model.  
22. Early diagnosis of invasive pulmonary aspergillosis in hematologic patients: an opportunity to improve the outcome.  
26. Isavuconazole (BAL4815) pharmacodynamic target determination in an in vivo murine model of invasive pulmonary aspergillosis against wild-type and cyp51 mutant isolates of Aspergillus fumigatus.  
28. The strategy for the diagnosis of invasive pulmonary aspergillosis should depend on both the underlying condition and the leukocyte count of patients with hematologic malignancies.  
29. Invasive pulmonary aspergillosis: prediction at thin-section CT in patients with neutropenia--a prospective study.  
30. Invasive aspergillosis in the immunocompromised host: utility of computed tomography and bronchoalveolar lavage.
5.1.5. Angioinvasive aspergillosis

- **Angioinvasive aspergillosis** is most aggressive form of aspergillosis, with a mortality rate that may exceed 50%.
- It occurs when the hyphae invade bronchial wall and subsequently the accompanying arterioles, with consequent thrombosis and the formation of necrotic hemorrhagic nodules or subpleural wedge-shaped hemorrhagic infarcts.
- It is seen almost exclusively in severely immunocompromised. Neutropenia is the most important risk factor, following by prolonged Corticosteroid therapy, transplantation, hematologic malignancy, Cytotoxic therapy and AIDS.
- Aspergillus may disseminate to another organs, most commonly to the brain (seizures, ring-enhancing lesions, cerebral infarctions, intracranial haemorrhage, meningitis and epidural abscess), skin, kidneys, heart, esophagus and liver.
- Radiographic abnormalities include single or multiple nodular infiltrates; segmental or subsegmental consolidation; diffuse ground-glass pattern (often progressing to consolidation) and cavitation (air-crescent sign); pleural effusions are uncommon.
- Chest CT scan may shows multiple nodules surrounded by areas of ground-glass attenuation known as halo sign and areas of segmental and non-segmental consolidation, which are often bilateral, with or without a halo. “The halo sign” represents haemorrhage around a pulmonary nodule and is highly suggestive of angioinvasive aspergillosis.
- Another finding are wedge-shaped areas of consolidation with a broad base abutting a peripheral pleural surface by hemorrhagic infarcts.
- The cavitation and “air crescent sign” are viewed when area of necrotic tissue is reabsorbed from the periphery, which causing retraction of the infarct from viable lung parenchyma and leaves a space of air surrounding. This air-space doesn’t change with position of patient and it’s different to monod sign of aspergilloma.

A typical image of Angioinvasive aspergillosis in a 45 year-old neutropenic patient after hematopoietic stem cell transplantation (HSCT), Tomas Franquet Casas, Hospital de Sant Pau in Barcelona
5.6. Aspergillus bronchitis and tracheobronchitis

- *Aspergillus* tracheobronchitis is defined as an *Aspergillus* infection which is limited entirely or predominantly confined to the tracheobronchial tree. In addition, Denning suggested the term be applied to patients in whom there is evidence of bronchial and/or tracheal inflammation, excess mucus production, with *Aspergillus* as the only pathogen and without invasion of bronchial mucosa on biopsy, but full criteria for this diagnosis have not been validated.

- *Aspergillus* infection of the large airways has several manifestations. Many authors try to propose a classification to describe the disease, but to date; there is still no ideal classification. Overlapping clinical features can make cases difficult to classify. Interestingly Young et al. described a non-invasive form of infection, with the bronchial mucosa is usually preserved, but this contrasts with many reported invasive cases in patients with immunosuppression and poor immunological host responses.

- *Aspergillus fumigatus* is the most common species being isolated (74-84%), followed with *Aspergillus flavus* (8-21%). Other *Aspergillus* species (3-5%) have also been isolated, such as *Aspergillus niger*, *Aspergillus terreus*, *Aspergillus nidulans* and *Aspergillus versicolor*.

- Wu et al.(2009) proposed a classification based on bronchoscopic morphology of the intraluminal lesions into four types: superficial infiltration type (Type I), full-layer involvement type (Type II), occlusion type (Type III) and mixed type (Type IV), then a mixed type which an overlapping bronchoscopic features seen in all morphological types.

1. **Superficial infiltration type**: Inflammatory infiltration, mucosa hyperaemia, mucosa oedematous and superficial ulcer which is confined to the mucosa and submucosa; mild plaques of pseudomembrane formation without obvious airway obstruction or deeper tissue invasion.

2. **Full-layer involvement type**: Tracheobronchial lesions infiltrating through the matrix layer of bronchi, often with substantial and deep ulceration,
extensive tissue necrosis with cartilage invasion and destruction of normal airway structures

3. **Occlusion type**: Airway obstruction or constriction > 50% of the original caliber of involved bronchi caused by extensive pseudomembrane formation, polypoid granulation or necrotic tissues as a result of *Aspergillus* infection, without definite proof of full-layer invasion.

4. **Mixed type**: Two or more different forms of typical bronchoscopic features coexisting at the time of diagnosis.

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**Recently reported cases:**

2. Ulcerative tracheobronchitis due to Aspergillus.  
3. Colonization with small conidia Aspergillus species is associated with bronchiolitis obliterans syndrome: a two-center validation study.  
4. [The aspergillus laryngotraceobronchitis. A case report and literature review].  
5. Aspergillus bronchitis without significant immunocompromise.  
6. Aspergillus tracheobronchitis in allogeneic stem cell transplanted recipient.  
7. [Aspergillus tracheobronchitis in a lung transplant recipient].  
10. Ulcerative and pseudomembranous Aspergillus tracheobronchitis in a patient with acute myeloid leukemia. 180
11. Aspergillus niger causing tracheobronchitis and invasive pulmonary aspergillosis in a lung transplant recipient: case report. 181
12. Ulcerative tracheobronchitis due to Aspergillus. 199
13. Tracheal oxalosis associated with Aspergillus niger tracheobronchitis. 200
14. Colonization with small conidia Aspergillus species is associated with bronchiolitis obliterans syndrome: a two-center validation study. 201
15. [The aspergillus laryngotracheobronchitis. A case report and literature review]. 202
16. Aspergillus bronchitis without significant immunocompromise. 203
17. Tracheobronchial Manifestations of Aspergillus Infections. 204
18. Pseudomembranous Aspergillus tracheobronchitis in a heart transplant recipient. 205
19. Isolated invasive Aspergillus tracheobronchitis: a clinical study of 19 cases. 206

5.1.7. Chronic cavitary pulmonary aspergillosis (CCPA)

- The commonest symptom complex consists of weight loss, chronic cough, hemoptysis, fatigue and shortness of breath.
- While the clinical signs and symptoms of CCPA are non-specific, their presence and severity is an important point of distinction from simple aspergilloma.
- Radiological examination usually reveals one or more cavities, typically within the upper lobes which may or may not contain fungus balls. New cavity formation or expansion of one or more existing cavities over time is highly characteristic.
- Peri-cavitary infiltrates and adjacent pleural thickening are frequently observed and appear to be indicative of disease activity; these radiological abnormalities may remit with effective antifungal therapy leaving residual thin-walled empty cavities.

Severe bilateral chronic pulmonary aspergillosis with the left upper lobe replaced by one large and several smaller cavities. w www.life-worldwide.org
Chronic cavitary pulmonary aspergillosis is a multicavitary disease in immunocompetent patients and progresses over time. Previous mycobacterium infection www.life-worldwide.org

Recently reported cases:

1. A prominent role for the IL1 pathway and IL15 in susceptibility to chronic cavitary pulmonary aspergillosis. 182
2. Pulmonary aspergillosis in an immunocompetent patient. 183
3. Itraconazole in chronic cavitary pulmonary aspergillosis: a randomised controlled trial and systematic review of literature. 184
4. Cavitary pulmonary lesion associated with Aspergillus fumigatus infection in a German shepherd dog. 185
5. Distinct alleles of mannose-binding lectin (MBL) and surfactant proteins A (SP-A) in patients with chronic cavitary pulmonary aspergillosis and allergic bronchopulmonary aspergillosis. 186
6. The efficacy and tolerability of voriconazole in the treatment of chronic cavitary pulmonary aspergillosis. 187

5.1.8. Disseminated aspergillosis (Invasive aspergillosis)

- Invasive aspergillosis is generally seen in severely immunocompromised individuals and carries a high mortality rate.
- Risk factors for invasive aspergillosis include neutropenia, immunosuppressive therapy, high-dose systemic corticosteroids, AIDS, solid organ transplant and haematopoietic stem cell transplant.
- The lungs are the most common site of primary invasive disease. The CNS is the most common secondary site of invasive disease.
- Invasive infections due to Aspergillus fumigatus are increasing, and despite new therapies, are associated with greater than 50% mortality.
- Invasion of blood vessels is a hallmark pathologic feature of invasive aspergillosis and plays a critical role in the development of local and disseminated disease.
- This process of angioinvasion and subsequent dissemination is unique to A. fumigatus and a handful of other pathogenic molds, and its mechanism is not well understood.
- Histopathologic studies suggest that there are several key steps by which the organism gains entry to and subsequently exits from the vascular system.
- Hyphae from an infectious focus must invade the abluminal surface of the blood vessel, and penetrate endothelial cells to gain access to the blood vessel lumen.
- Hyphal fragments are borne by the bloodstream to distal sites where they adhere to and penetrate the luminal surface of the endothelial cells lining the blood vessel and thereby invade the deep organs.
- It is hypothesized that the interactions of A. fumigatus with the vascular endothelium are critical to the pathogenesis of invasive aspergillosis.
Recently reported cases:
1. Primary gut aspergillosis in a patient with acute myeloid leukaemia: the importance of early suspicion and definitive treatment. 188
2. Disseminated aspergillosis as the herald manifestation of chronic granulomatous disease in an adult patient. 189
3. Immune reconstitution syndrome-like entity in lung transplant recipients with invasive aspergillosis. 190
4. Aspergillus felis sp. nov., an emerging agent of invasive aspergillosis in humans, cats, and dogs. 191
5. [Mixed invasive fungal infection due to Rhizomucor pusillus and Aspergillus niger in an immunocompetent patient.] 192
6. [An autopsy case of ulcerative colitis with disseminated aspergillosis, complicated by brain hemorrhage]. 193
7. Invasive aspergillosis masquerading as catastrophic antiphospholipid syndrome. 194
8. Disseminated Aspergillosis due to Aspergillus niger in Immunocompetent Patient: A Case Report. 195
9. Clinical experience in invasive fungal infections: multiple fungal infection as the first presentation of HIV. 196
10. Pharmacodynamics and dose-response relationships of liposomal amphotericin B against different azole-resistant Aspergillus fumigatus isolates in a murine model of disseminated aspergillosis. 197
11. Systemic dissemination of chronic necrotizing pulmonary aspergillosis in an elderly woman without comorbidity: a case report. 198
5.2. Cerebral aspergillosis

- Cerebral Aspergillosis is the most lethal manifestation of infection due to Aspergillus species arising most commonly as hematogenous dissemination from a pulmonary focus, direct extension from paranasal sinus infection or direct inoculation through trauma and surgery of the central nervous system (CNS).
- Meningitis is rare and spinal cord involvement is barely reported.
- It has non-specific clinical presentation and non-specific radiological abnormalities
- Cerebral aspergillosis in the immunocompromised host is often not diagnosed until autopsy, and carries a mortality of about 99%.
- In the non-immunocompromised patient cerebral aspergillosis is rare.
Recently reported cases:

1. Improving Outcomes in Cerebral Aspergillosis. World Neurosurg. 207
2. High weekly doses of liposomal amphotericin B as secondary prophylaxis after cerebral aspergillosis in a paediatric patient. 208
3. Striated enhancement sign in invasive cerebral fungal granuloma by Aspergillus: a case report. 209
4. Cerebral aspergillosis in adult critically ill patients: a descriptive report of 10 patients from the AspICU cohort. 210
5. A Case of Acute Cerebral Aspergillosis Complicating Influenza A/H1N1pdm 2009. 211
6. Cerebral aspergillosis and acute myeloid leukemia. 212
7. Pituitary aspergillosis in a kidney transplant recipient and review of the literature. 213
8. Isolated Cerebral Aspergillosis in Immunocompetent Patients. 214
9. Aspergillus brain abscess. 215
10. Cerebral aspergillosis with multiple enhancing nodules in the right cerebral hemisphere in the immune-competent patient. 216
11. Unusual case of cerebral aspergillosis with clinical and imaging findings mimicking lymphoma. 217
12. Early diagnosis of cerebral aspergillosis with various methods: a case report. 218
13. Cerebral aspergillus infection in pediatric acute lymphoblastic leukemia induction therapy. 219
14. Aspergillus galactomannan antigen for diagnosis and treatment monitoring in cerebral aspergillosis. 229
15. Cranial aspergilloma masquerading as meningioma. 221
16. Antifungal therapy of aspergillosis of the central nervous system and aspergillus endophthalmitis. 222
17. Fatal case of cerebral aspergillosis: a case report and literature review. 223
18. Central nervous system aspergillosis: a series of 14 cases from a general hospital and review of 123 cases from the literature. 224
19. Relapsing cerebral aspergilloma associated with pregnancy. 225
20. Treatment of refractory cerebral aspergillosis in a liver transplant recipient with voriconazole: case report and review of the literature. 226

5.3. Cutaneous aspergillosis

- Cutaneous aspergillosis has been described as primary or secondary to haematogenous dissemination.
- Primary cutaneous aspergillosis usually follows local trauma and appears as a purplish oedematous lesion at the site of inoculation. Primary cutaneous aspergillosis is a rare disease usually caused by Aspergillus fumigatus, Aspergillus flavus, Aspergillus terreus and Aspergillus ustus.
- It is usually seen in immunocompromised hosts, though some cases are also reported in immunocompetent hosts.
- It usually develops in relation to local trauma (intravenous injection site, injury or burns).
- Clinically, it is characterized by the presence of violaceous macules, papules, haemorrhagic bullae, ulcerations with central necrosis, and pustules or subcutaneous abscess.
- The occurrence of varying clinical manifestations of fungal diseases has been demonstrated in patients with altered host defences. Immunocompromised patients with primary cutaneous aspergillosis occasionally present with solitary non-ulcerated nodules.

Multiple cutaneous lesions on the leg in a case of disseminated aspergillosis due to A. fumigatus.

Punch biopsied specimen of skin shows acute and chronic inflammation with hyaline, septated, and acute-angle branched hyphae invading vessels in dermis and subcutis (A) Periodic acid Schiff (H&E stain, ×400), (B) Grocott-Gomori methenamine silver (H&E stain, ×400). Jin-Hee No et al., Infect Chemother. 2010 Aug;42(4):244-248.

Recently reported cases:
1. Aspergillus fumigatus infection on a home-made tattoo. 227
2. What is your diagnosis? primary cutaneous aspergillosis. 228
3. Fatal-mixed cutaneous zygomycosis-aspergillosis: a case report. 229
4. SPrimary cutaneous aspergillosis due to Aspergillus tamarrii in an immunocompetent host. 230
5. A case of dual infection in a paediatric trauma victim of primary cutaneous aspergillosis caused by Aspergillus flavus and Aspergillus terreus. 231
6. [Primary cutaneous aspergillosis in an extremely low birth weight preterm infant]. 232
7. Primary cutaneous aspergillosis complicating tumor necrosis factor-α blockade therapy in a patient with psoriasis. 233
8. Post-filarial cutaneous aspergillosis. 234
9. Cutaneous aspergillosis associated with HIV infection. 235
10. Primary Cutaneous Aspergillosis Complicating Tumor Necrosis Factor-α Blockade Therapy in a Patient With Psoriasis. 236
11. Primary cutaneous aspergillosis in two pediatric trauma patients. 237
12. Primary cutaneous aspergillosis from Tamilnadu diagnosed by fine needle aspiration cytology. 238
13. Primary cutaneous aspergillosis in a patient with systemic lupus erythematosus. 239
14. [Case of primary cutaneous Aspergillus caldioustus infection caused by nerve block therapy]. 240
15. Severe cutaneous aspergillosis in a premature neonate linked to nonsterile disposable glove contamination? 241
16. Investigation of a cluster of cutaneous aspergillosis in a neonatal intensive care unit. 242
17. Nonhealing scalp wound infected with Aspergillus niger in an elderly patient. 243
18. Tracheobronchial aspergillosis following primary cutaneous aspergillosis in a lung-transplant recipient. 244
19. [Posttraumatic primary cutaneous aspergillosis with Candida guilliermondii infection in a healthy host]. 245
20. Primary cutaneous aspergillosis. 246
21. A Case of Disseminated Aspergillosis Presenting Solely as Multiple Cutaneous Lesions in an Acute Leukemia Patient, 247

5.4. Aspergillus Onychomycosis

- Many different species of Aspergillus may cause onychomycosis including A. niger, A. fumigatus, A. versicolor, A. terreus and some rare species.
- Among non-dermatophyte mould onychomycosis, proportional rates of Aspergillus onychomycosis vary from 5% to as high as 30%
- There are 2 common patterns of disease, destructive and superficial white onychomycosis, but lateral and distal onychomycosis may also be seen.
- Particular features suggestive of Aspergillus infection are a chalky, deep white nail with early involvement of the lamina and painful perionyxis without pus.
- Trauma is the common predisposing factor. The affected nail is most often a toenail; peripheral vascular disease is occasionally implicated.
5. Ocular aspergillosis

- Presence of fungus in the conjunctiva is a constant threat to the eyes, because these microorganisms, defined as opportunistic, may provoke severe ocular infections, in situations as low organic resistance, use of immunosuppressants, antibiotics and epithelial alteration.
- Aspergillus species have been implicated in a wide variety of primary ocular conditions, characterized by either slow and asymptomatic infection, or rapid, uncontrollable progression and sometimes death.
- Endogenous Aspergillus endophthalmitis is most commonly reported in immunosuppressed patients with organ transplants or after valve replacement and in individuals suffering from hematological malignancies. It may also be the presenting feature of disseminated aspergillosis.
- *Aspergillus* keratitis is an important ophthalmological problem worldwide, but especially in outdoor workers in agricultural communities in the developing world and in tropical and subtropical areas, where it frequently occurs following traumatic inoculation of *Aspergillus* conidia into the cornea through injury.
- In recent years, *Aspergillus* keratitis has been reported to occur following ocular surgical procedures, such as radial keratotomy, laser-assisted in situ keratomileusis and keratoplasty.
- *Aspergillus* keratitis is a medical emergency, since the patient frequently presents with extreme pain and loss of vision, and needs to be recognized and treated promptly.
- *fumigatus* is the commonest cause of *Aspergillus* keratomycosis. In recent years, other species, particularly *Aspergillus flavus*, have been reported to predominate in *Aspergillus* keratitis.

Aspergillus keratitis in patient from Pakistan

Shrunken eye as a consequence of this infection

Dr Andrew Tullo, Royal Eye Hospital, Manchester
• Severe aspergillus infection with large area of corneal ulceration and deep stromal involvement
• Severe central aspergillus infection with a “cheesey” looking area of the lesion and hypopyon (fluid level of inflammatory cells in the anterior chamber)

Bilateral \( A. \text{fumigatus} \) endophthalmitis in association with pulmonary and cerebral aspergillosis, complicating severe autoimmune disease treated with intense immunosuppression. Dr Richard Wintle and Dr Steven Charles, Royal Eye Hospital, Manchester, UK

Recently reported cases:

1. Aspergillus terreus endogenous endophthalmitis in a nonimmunocompromised patient with a history of bronchiectasis.\(^\text{248}\)
2. Epidemiology of Aspergillus keratitis at a tertiary care eye hospital in South India and antifungal susceptibilities of the causative agents.\(^\text{249}\)
3. Aspergillus endophthalmitis in one eye subsequent to bilateral anterior chamber phakic intraocular lens implantation.\(^\text{250}\)
4. Ocular aspergillosis: Obtaining a specimen is crucial for diagnosis. A report of three cases.\(^\text{251}\)
5. Detection of Candida and Aspergillus species DNA using broad-range real-time PCR for fungal endophthalmitis.\(^\text{252}\)
6. Molecular characterization of drug-resistant and drug-sensitive Aspergillus isolates causing infectious keratitis.\(^\text{253}\)
7. Aspergillus keratitis in vernal shield ulcer--a case report and review.\(^\text{254}\)
8. Mycotic keratitis due to Aspergillus nomius.\(^\text{255}\)
9. Infectious keratitis caused by Aspergillus tubingensis.\(^\text{256}\)
10. \( A. \text{flavus} \) keratomycosis in a cat treated with topical 1% voriconazole solution.\(^\text{257}\)
5.6. Aspergillus sinusitis

- *Aspergillus* disease can happen in the sinuses leading to *Aspergillus* sinusitis. Just as in the lungs, *Aspergillus* can cause the three diseases - allergic sinusitis, a fungal ball or invasive aspergillosis. Allergic disease is associated with long standing symptoms of a runny blocked up nose, and may lead to nasal polyps.
- The fungal ball caused by *Aspergillus* happens in a similar way to an aspergilloma. In those with normal immune systems, stuffiness of the nose, chronic headache or discomfort in the face is common.
- When patients have damaged immune systems - if, for example they have had leukaemia or have had a bone marrow transplant - *Aspergillus* sinusitis is more serious. In these cases the sinusitis is a form of invasive aspergillosis. The symptoms include fever, facial pain, nasal discharge and headaches.

![Base of skull at autopsy showing pus in the sphenoid sinus and destruction of the lateral wall of the sinus, as demonstrated on the CT scan. Cultures from the sinus and brain abscess grew Aspergillus fumigatus.](https://www.njmoldinspection.com)

Recently reported cases:

1. [Allergic fungal sinusitis--new aspects of clinical features, laboratory diagnosis and therapy].
3. Mycotic aneurysm due to Aspergillus sinusitis.
4. Coexistence of allergic bronchopulmonary aspergillosis and allergic aspergillus sinusitis in a patient without clinical asthma.
5. [Clinicopathologic study of invasive fungal rhinosinusitis caused by Aspergillus and Mucorales].
6. [Cellular and tissue reactions of the mucous membrane of the maxillary sinus in the patients presenting with odontogenic aspergillous maxillary sinusitis].
7. [Application of PCR combined with reverse line blot assay in detection and identification of common pathogenic Aspergillus in fungal sinusitis].

78
5.7. Paranasal sinuses aspergillosis

- Paranasal sinus Aspergillosis is now classified into invasive (acute fulminant, chronic invasive, granulomatous invasive) and non-invasive (fungus ball and allergic fungal rhinosinusitis) forms with their own pathophysiology and clinical presentation.
- Any type of paranasal Aspergillosis may progress to more aggressive disease illustrating the importance of early recognition of this increasingly encountered disease.
- Prerequisites for diagnosis are sinonasal polyps, infiltrative or non-infiltrative fungal hyphae on microscopy with Potassium Hydroxide (KOH) and histopathological examination of the resected polyps and positive fungal culture of the tissue following surgery.
- Intracranial spread of the infection occurs due to close proximity of the sinuses with cranial cavity. It is a dreaded complication, as it is usually fatal if not treated promptly.
- Orbital involvement occurs by contiguous spread of the disease from paranasal sinuses, by expansion or bone erosion due to pressure effect of the polyps or fungal tissue invasion.
- It is considered to worsen the prognosis of sinonasal aspergillosis. Moreover, the superior orbital fissure and optic canal directly open into the middle cranial fossa, and are ready pathways for further intracranial spread of the infection.

Left: Double density sign (white arrows) of non-invasive aspergillus infection of paranasal sinuses on coronal contrast enhanced CT scan. Right: Extensive sino-nasal polyposis (white arrow) involving all sinus cavities and nose on coronal contrast enhanced CT scan.
Sections of the maxillary sinus show (a) Aspergillus in necrotic background (H and E, ×250), (b) fungal hyphae in giant cell (H and E, ×400), (c) many eosinophils and hyphae (H and E, ×250), special stains highlighting the fungal morphology (d; PAS, ×250) and (e; silver methanamine, ×250). Divya Sharma, Nidhi Mahajan, Seema Rao, Nita Khurana, Shyama Jain, Department of Pathology, Maulana Azad Medical College, New Delhi, India

**Recently reported cases**
1. Diagnosis and treatment of paranasal sinus fungus ball of odontogenic origin: case report.  
2. Computed tomographic features of feline sino-nasal and sino-orbital aspergillosis.  
3. Granulomatous invasive aspergillosis of paranasal sinuses masquerading as actinomycosis and review of published literature.  
5. [Allergic fungal sinusitis--new aspects of clinical features, laboratory diagnosis and therapy].  
6. [Invasive aspergillosis of sphenoidal sinus in a patient in Djibouti, revealed by palsy of cranial nerves: a case report].  
7. Invasive fungal rhinosinusitis.  
8. [Unilateral frontal sinus aspergillosis: the combined endoscopic and mini-trephination approach].  
11. Highly effective unconventional management of aspergillosis of the left maxillary sinus in an 11-year-old girl with rhabdomyosarcoma embryonale of the frontal sinus.  
12. [Chronic diseases of the nose and nasal sinuses in cats: a retrospective study].  
13. Simultaneous actinomycosis with aspergillosis in maxillary sinus.  
14. Clotrimazole and enilconazole distribution within the frontalsinuses and nasal cavity of nine dogs with sinonasal aspergillosis.
5.8. Otoaspergillosis (Otomycosis)

- Otomycosis is subacute or chronic superficial fungal infection of the external auditory canal and auricle. It is the most frequently encountered fungal infection in ear, nose and throat clinics. The fungi are usually secondary invaders of tissue already rendered susceptible by bacterial infections, physical injury or excessive accumulation of cerumen in the external auditory canal. Sometimes it is merely non-pathogenic fungal colonization of the external auditory canal.
- The disease is worldwide in distribution. Otomycosis is more prevalent in warm, humid climates, particularly in the rainy season as compared to arid or cold climates. It is more frequent in individuals of lower socio-economic status with poor hygienic conditions.
- There are many local predisposing factors of otomycosis such as chronic infection of the ear, use of oils, ear-drops, steroids, swimming and evidence of fungal infection elsewhere. Local lesions observed in bacterial otitis create favourable conditions for the growth of fungi in the external and middle ear, as well as in post-operative cavities, especially in cases of open-type surgery. Persistent wetness of the external auditory canal predisposes to fungal
- In about 75-92% cases of otomycosis, *Aspergillus* genus alone is the causative agent. *A. niger* is the most common cause, with occasional cases caused by *A. flavus* and *A. fumigatus*.
- Otomycosis usually presents with a history of itching, irritation, discomfort, pain and scanty discharge from the affected ear. There is also a feeling of blockage in the ear due to collection of debris material in external auditory canal. Irritation is more marked in fungal as compared to bacterial otitis externa. Pruritus and discharge are the most common symptoms, with reddened epidermis and lining of the tympanic cavity being common.
- Otoscopic examination reveals infection confined to the ear canal. There is greenish or black fuzzy growth on cerumen or debris resembling wet ‘blotting paper’, which may fill up the entire meatus. There may be slight conduction deafness also due to mechanical obstruction of the external auditory canal. The local area may be hyperemic and sometimes bleeding may be observed. In immunocompromised patients especially diabetics, *Aspergillus* may invade locally to adjacent anatomical sites like mastoid bone or even brain.
- *Aspergillus* may cause invasive external otitis (necrotizing or malignant otitis externa) with local spread to bone and cartilage, which is a severe and potentially life-threatening disease. This may be associated with underlying immunocompromised situation, diabetes mellitus or patient receiving haemodialysis entailing high mortality. Invasive otitis externa is more frequently caused by *A. fumigatus* than *A. niger*. In addition,
invasive *Aspergillus* tympanomastoiditis may be encountered in immunocompetent patients as well.

**Recently reported cases**

1. Otomycosis in the north of Iran: common pathogens and resistance to antifungal agents. Eur Arch Otorhinolaryngol. 281
2. Prevalence of otomycosis in Khouzestan Province, south-west Iran. 282
3. Otomycosis in central Iran: a clinical and mycological study. 283
4. Otomycosis in immunocompetent and immunocompromised patients: comparative study and literature review. 284
5. Molecular identification and antifungal susceptibilities of black Aspergillus isolates from otomycosis cases in Hungary. 285
6. Species assignment and antifungal susceptibilities of black aspergilli recovered from otomycosis cases in Iran. 286
7. Otomycosis due to filamentous fungi. 287
8. Prevalence of otomycosis in Ibadan: a review of laboratory reports. 288
9. Otomycosis: Diagnosis and treatment. 289

**5.9. Aspergillus endocarditis**

- Most cases of *Aspergillus* endocarditis (AE) involve adults.
- Pre-requisites for developing AE. are valvular anatomic abnormalities, rheumatic heart disease, previous bacterial endocarditis, previous surgery.
- Conditions that predispose to invasive fungal infections (eg malignancy, antimicrobial use, neutropenia, injecting drug use and immunosuppressive states and therapy) are also commonly found in AE.
• Diagnosis of AE is difficult and frequently delayed: the diagnosis is made post-mortem. Blood cultures are almost always negative. Mycological examination of vegetations or emboli is the most common means of diagnosis.

• Crude mortality from FE in general is around 72% although in recent years this has dropped to around 59%. For AE the mortality rate was 68% (McCormack, 2010). The cause of death is directly attributable to *Aspergillus* in 90% of cases and is usually due to catastrophic valvular failure or complications secondary to major embolic phenomena: usually cerebral.

**Recently reported cases:**

1. Aspergillus endocarditis in a paediatric patient after a cardiac surgery, associated with septic pulmonary embolism and pulmonary hypertension. 290

2. Isolated aspergillosis myocardial abscesses in a liver-transplant patient. 291

3. Acute myocardial infarction caused by coronary embolism from Aspergillus endocarditis. 292

4. Aspergillus pacemaker lead endocarditis. 293

5. Fungal endocarditis. 294


7.  

   . [Aspergillus prosthetic aortic valve endocarditis; report of a case]. 296

8. Aspergillus endocarditis in lung transplant recipient: successful surgical treatment. 297

9. The tell-tale heart: Aspergillus fumigatus endocarditis in an immunocompetent patient. 298

10. Aspergillus endocarditis in the era of new antifungals: major role for antigen detection. 299

11. A Report of 2 Cases of Disseminated Invasive Aspergillosis with Myocarditis in Immunocompromised Patients. 300

12. Aspergillus endocarditis in a native valve without prior cardiac surgery. 301

13. Aspergillus endocarditis: a case of near complete left ventricular outflow obstruction. 302

14. NikoTwo cases of aspergillus endocarditis in non neutropenic children on chemotherapy for acute lymphoblastic leukaemia. 303

15. Infective endocarditis due to Aspergillus following kidney transplantation. 304

16. Molecular diagnosis of Aspergillus fumigatus endocarditis. 305

17.  

   . Cardiac aspergillosis: endocardial or endomyocardial? 306

18. [Cardiac invasive aspergillosis in a heart transplant recipient]. 307
Invasion of the thyroid gland is common in disseminated invasive aspergillosis. Patients typically present with fever and tender thyroid enlargement, involving one or both lobes. Clinically the thyroid may be diffusely enlarged or a nodule may be palpable. Marked thyroid enlargement leading to fatal airway obstruction has been described, as has compression of the oesophagus leading to dysphagia. Histology of thyroid tissue usually demonstrates abscesses containing necrotic debris, haemorrhage and Aspergillus hyphae. Vascular invasion with thrombosis and infarction is sometimes prominent.

Recently reported cases:

1. Aspergillus thyroiditis: a review of the literature to highlight clinical challenges.
2. Rapidly growing thyroid mass in an immunocompromised young male adult.
4. Successful treatment of acute thyroiditis due to Aspergillus spp. in the context of disseminated invasive aspergillosis in a kidney transplant patient.
5. Aspergillus thyroiditis in a renal transplant recipient mimicking subacute thyroiditis.
6. Aspergillus thyroiditis in a living donor liver transplant recipient.
7. Aspergillus thyroiditis.

Aspergillus hyphae with septae, branching at 45° (PAS)

Aspergillus hyphae with septae, branching at 45° (PAS)
5.11. Hepatic aspergillosis

- Liver transplant recipients are at high risk of infection with *Aspergillus* species, which may cause invasive disease and severe complications in this patient population.
- There is a high incidence of invasive aspergillosis (IA) in liver transplant recipients.
- The mortality of IA in liver transplant recipients is approximately 90%.
- Invasive pulmonary aspergillosis is most common but disseminated disease occurs in ~50% of liver transplant recipients affected.

A 52-year-old woman; status after bone marrow transplantation for acute myelogenous leukemia with ringenhancing lesions in the liver and spleen caused by aspergillosis fungal infection. Marchelle J. Bean, MD, Karen M. Horton, MD, and Elliot K. Fishman, MD, J Comput Assist Tomogr 2004;28

Left: chronic hepatic aspergilloma with central necrosis surrounded by few Giant cells (arrows) and fibrotic wall (HE ×125) Right: active hepatic abscess showing giant cells with negative profiles of fungal hyphae (arrows) surrounded by inflammatory cells (PAS × 325)., Gupta KL, Rajaram K G, Joshi K, Sakuja V. Indian J Pathol Microbiol 2012;55:580-2
Recently reported cases:

1. Primary hepatic aspergillosis following induction chemotherapy for acute leukemia. 317
2. Progression of hepatic aspergillosis following second renal transplantation in a patient with recurrent glomerulonephritis. 318
3. Invasive aspergillosis in patients with severe alcoholic hepatitis. 319
4. Aspergillosis after liver transplantation in the context of common variable immunodeficiency: case report. 320

5.12. Gastrointestinal aspergillosis

- There are few reports in the literature of gastrointestinal aspergillosis without pulmonary involvement as the initial presentation of disseminated disease.
- Tumour-like masses (aspergillomas) in the gastrointestinal tract have been very rarely reported.
- The port of entry is usually the lungs and wide dissemination is possible after vascular invasion.
- The gastrointestinal tract may be involved via oesophageal or bowel ulceration, especially in the immunocompromised host.
- Necrotizing enterocolitis may precede aspergillosis and disruption of mucosal barriers may provide a port of entry for germinating spores.
- The features of gastrointestinal tract involvement are mild anaemia, weight loss, diarrhoea with malabsorption, in the absence of any other cause for the diarrhoea, gastrointestinal haemorrhage and a swinging fever not responding to antibiotics. Occasionally, there may by signs of peritonitis, especially if there is bowel perforation or infarction.
- Gastrointestinal haemorrhage is a known complication of aspergillus infection of the gut. This may be due to gut infarction, colonic or duodenal ulceration.
- Uncontrollable upper gastrointestinal bleeding due to erosion into the descending aorta, resulting in a rapidly fatal outcome, has been reported in oesophageal aspergilloma.

Recently reported cases:

1. Primary gastrointestinal aspergillosis 6 months after allogeneic hematopoietic cell transplantation: a case report. 321
2. Invasive Aspergillus infection localized to the gastric wall: report of a case. 322
3. A retrospective series of gut aspergillosis in haematology patients. 323
4. A case of isolated invasive Aspergillus colitis presenting with hematochezia in a nonneutropenic patient with colon cancer. 324
5. Necrotizing colitis caused by systemic aspergillosis in a burn patient. 325
6. Successful treatment of acute thyroiditis due to Aspergillus spp. in the context of disseminated invasive aspergillosis in a kidney transplant patient. 326
5.13. Urinary tract aspergillosis

- Aspergillosis limited to the urinary tract is a rare disease, often occurring in immunocompromised patients.
- Three different patterns of renal *Aspergillus* infection have been: disseminated aspergillosis with hematogenous renal involvement, aspergillosis of the renal pelvis with bezoars formation, and ascending panurothelial aspergillosis. Extrarenal aspergillosis of the urinary tract is sparse, with few cases of testicular and adrenal involvement being described.
- The kidney is the most frequently involved part of the urinary tract in invasive aspergillosis.
- Both bladder and prostate aspergillosis are also described.
- Outflow obstructive symptoms, similar to those due to benign prostate hypertrophy (BPH) are predominant. Other related symptoms could be dysuria, perineal or suprapubic discomfort and hematuria.
- The prostate fungal infection is indistinguishable from BPH, bacterial and tuberculosis prostatitis or malignancy of the gland. Prolonged courses of antibiotics, steroid intake and an indwelling bladder catheter have been identified as presumed predisposing factors in these cases.
- Renal involvement is usually silent if the disease is localised to the cortex of the kidney and is a relatively frequent finding at autopsy in the context of disseminated disease.
- Despite the increased incidence of invasive aspergillosis in transplant recipients, urinary tract infections caused by *Aspergillus* species are uncommon and usually as a consequence of a systemic haematogenous dissemination, characterized by multiple parenchymal microabscesses.
- More common, although still rare, is renal pelvis involvement. Involvement may be unilateral or bilateral. Typical host groups include diabetics and intravenous drug abusers. Fungal masses (bezoars) fill the pelvis of the kidney causing hydronephrosis. These masses may be passed in the urine as `balls' and may cause renal colic.
- Anuria due to bilateral ureteral obstruction with mycelial clumps, although rare, has been recently reported. *Aspergillus* is usually cultured from the urine and can be cultured and visualised in the fungal balls.

Recently reported cases:

1. An unusual case of non-disseminated bladder aspergillosis in a setting of transitional cell carcinoma. 327
2. Nosocomial urinary tract aspergillosis in an immunocompetent host: an unusual occurrence. 328
3. Localized primary renal aspergillosis in a diabetic patient following lithotripsy--a case report. 329
4. An unusual cause of ureteral obstruction in a renal transplant recipient: ureteric aspergillosis. 330
5. Aspergillus in a cervico-vaginal smear of an adult postmenopausal female: An unusual case. 331
6. Isolated bladder aspergillosis as the primary presentation of non-oliguric acute renal failure. 332
5.13. *Aspergillus* osteomyelitis

- *Aspergillus* osteomyelitis is an uncommon manifestation of invasive aspergillosis. It may involve bones of the axial or appendicular skeleton.
- *Aspergillus* osteomyelitis is a particularly important cause of morbidity and mortality in immunocompromised hosts, especially in patients with chronic granulomatous disease, solid organ transplantation (SOT) and hematopoietic stem cell transplantation (HSCT), diabetes mellitus, and chronic corticosteroid use. Furthermore, *Aspergillus* osteomyelitis also is reported in alcoholics and illicit intravenous drug use. Notably, *Aspergillus* osteomyelitis is reported in patients without apparent immunodeficiency.
- Symptoms and signs of *Aspergillus* osteomyelitis tend to be non-specific.
- Histopathology and microbiologic examination of bone tissue biopsy are the gold standards for identification of *Aspergillus* spp.
- **Vertebral osteomyelitis** with or without discitis is the most common osteoarticular manifestation of *Aspergillus*. It may be caused by hematogenous dissemination from a distant site, by traumatic or surgical inoculation, or more rarely, from adjacent tissues, usually lungs. Host factors associated with *Aspergillus* vertebral osteomyelitis include chronic granulomatous disease, primary monocyte killing deficiency, chronic obstructive pulmonary disease treated with inhaled or systemic corticosteroids, intravenous corticosteroid treatment, solid organ transplantation, HSCT, diabetes mellitus, hematological malignancies, illicit intravenous drug use, pulmonary aspergillosis, and prior back surgery.
- **Sternal aspergillosis** is strongly associated with thoracic surgery. The route of infection is likely through direct inoculation of the wound through surgery, post-operative wound care or airborne transmission of conidia. *Aspergillus* sternal osteomyelitis may present in the immediate post-operative period, or later in the ensuing weeks, months, or even years after the operation.
- **Osteomyelitis of the Ribs and Long Bones** is common in patients with chronic granulomatous disease, immunosuppressed recipients of solid organ transplants and individuals who have experienced traumatic or surgical inoculation of affected bones.
Primary rib and long bone aspergillosis in immunocompetent individuals may rarely occur.

- **Invasive Aspergillus mastoiditis** may develop as an extension of infection from the middle ear into the mastoid process, petrous and temporal bones. It is characterized by otalgia, otorrhea, hearing loss and cranial nerve deficits, *Aspergillus* mastoiditis may be indolent or rapidly progressive. Chronic fungal otitis media and regional surgical procedures may progress to **invade** the petrous bone, transverse venous sinus, and the cranial nerves, resulting in sinus thrombosis, cranial nerve palsies, and high mortality.

- **Aspergillus osteomyelitis of the cranium and mandible** may occur as a sequela of other infectious processes, e.g., invasive *Aspergillus* otitis or sinusitis. There are different routes via which *Aspergillus* may invade the temporal bone and lateral skull base, such as the external ear or the tympanic cavity during the process of acute or chronic otitis media. Aspergillosis of the skull may also develop secondary to traumatic or surgical inoculation.

- **Joint space infection caused by Aspergillus spp. (Septic arthritis)** is uncommon. Septic arthritis may be subsequent to hematogenous dissemination of pulmonary aspergillosis, dissemination from adjacent bone tissue infection, or associated with traumatic or surgical manipulation. *Aspergillus* septic arthritis is commonly associated with intra-articular corticosteroid injections and orthopedic hardware. Other host factors that may exist simultaneously, with or independent of iatrogenic inoculation of *Aspergillus* into the joint, include malignancy and its management, neutropenia, solid organ or HSCT receipt, GVHD, alcoholic cirrhosis, and chronic granulomatous disease. *Aspergillus* septic arthritis rarely occurs in an otherwise healthy host, independent of any potential iatrogenic inoculation. Aspergillosis of the joint space also may occur in the context of disseminated aspergillosis.

Axial high-resolution computed tomography scan of temporal bone demonstrating R (right) - soft tissue lesion (*) involving the tympanic membrane (TM) and external auditory canal (EAC) L (left) - soft tissue lesion (a) involving the TM and EAC with erosion of posterior canal wall and facial canal near 2nd genu (b). Bradoo RA, Shah KD, Gayathri H, Kapadia MA. Invasive aspergillosis of the temporal bone. Indian J Otol 2012;18:30-3
Recently reported cases:

1. A rare case of spontaneous Aspergillus spondylodiscitis with epidural abscess in a 45-year-old immunocompetent female.\textsuperscript{341}
2. Does surgery influence the outcome of Aspergillus osteomyelitis?\textsuperscript{342}
3. Osteomyelitis caused by Aspergillus species.\textsuperscript{343}
4. Sternal osteomyelitis caused by Aspergillus fumigatus following cardiac surgery: Case and review.\textsuperscript{344}
5. Aspergillosis of bones and joints - a review from 2002 until today.\textsuperscript{345}
6. Aspergillus osteomyelitis: epidemiology, clinical manifestations, management, and outcome.\textsuperscript{346}
7. Costochondritis caused by Aspergillus flavus following cardiac surgery.\textsuperscript{347}
8. Osteomyelitis caused by Aspergillus species: a review of 310 reported cases.\textsuperscript{348}
9. Case report of Aspergillus osteomyelitis of the ribs in an immunocompetent patient.\textsuperscript{349}
10. A case-based discussion on a patient with non-otogenic fungal skull base osteomyelitis: pitfalls in diagnosis.\textsuperscript{350}
11. Vertebral osteomyelitis and epidural abscess due to Aspergillus nidulans resulting in spinal cord compression: case report and literature review.\textsuperscript{351}
12. Involvement of the opportunistic pathogen Aspergillus tubingensis in osteomyelitis of the maxillary bone: a case report.\textsuperscript{352}
13. Aspergillus osteomyelitis of the proximal humerus: a case report.\textsuperscript{353}
14. Aspergillus vertebral osteomyelitis in immunocompetent patients.\textsuperscript{354}
15. Skull base osteomyelitis and potential cerebrovascular complications in children.\textsuperscript{355}
16. Aspergillus osteomyelitis of the lumbar spine complicated with orbital apex syndrome: A potential role of the Batson's plexus in disease propagation.\textsuperscript{356}
17. Successful treatment of Aspergillus flavus spondylodiscitis with epidural abscess in a patient with chronic granulomatous disease.\textsuperscript{357}
18. Aspergillus fumigatus spondylodiskitis in renal transplant patient: voriconazole experience.\textsuperscript{358}
19. Osteomyelitis due to Aspergillus species in chronic granulomatous disease: an update of the literature.\textsuperscript{359}
20. Aspergillus vertebral osteomyelitis and ureteral obstruction after liver transplantation.\textsuperscript{360}
21. Aspergillus fumigatus osteomyelitis in a patient receiving alemtuzumab for B-cell chronic lymphocytic leukaemia.\textsuperscript{361}
22. Aspergillus vertebral osteomyelitis in immunocompetent hosts: role of triazole antifungal therapy.\textsuperscript{362}
6. Aspergillosis in animals

6.1. Aspergillosis in dogs

In dogs, the three major forms of aspergillosis are nasal, bronchopulmonary, and disseminated infections.

1. Nasal aspergillosis
   - Nasal aspergillosis frequently accompanied by invasive sinusitis, occurs most commonly in medium to large, dolichocephalic or mesaticephalic breeds.
   - The primary etiologic agent is A. fumigatus, followed by A. flavus and A. niger.
   - The clinical signs include sneezing, unilateral or bilateral nasal discharge, rhinalgia, epistaxis, frontal sinus osteomyelitis, anorexia, and lethargy. In advanced cases, ulceration of the nares, facial deformity due to paranasal extension, and ocular involvement may be evident.
   - Radiographs may show turbinate tissue destruction with large radiolucent spaces. Fungal plaques in the nasal cavity may be observed by rhinoscopy.

2. Bronchopulmonary aspergillosis
   - Bronchopulmonary aspergillosis is a rare disease in dogs.
   - The causative agents and the breeds being affected are similar to those seen in the nasal form of aspergillosis.
   - The clinical signs are nonspecific, including depression, fever, and cough. Chest radiographs can demonstrate diffuse nodular lesions in the lung.

3. Disseminated aspergillosis
   - Disseminated aspergillosis is a relatively infrequent but potentially fatal disease in dogs.
   - The two most common etiologic agents are A. terreus and A. deflectus, followed by A. fumigatus, A. niger, and A. flavipes in order of decreasing frequency.
   - The majority of the reported cases of disseminated aspergillosis in dogs involve young to middle-aged females.
   - The German shepherd dog is the most commonly affected breed; however, other breeds, including the Dalmatian, English setter, pug, Rhodesian ridgeback, springer spaniel, and whippet, have occasionally been affected.
   - Clinical signs of disseminated aspergillosis may develop suddenly or slowly over a few months.
   - Clinical presentations of disseminated aspergillosis may include diskospondylitis, osteomyelitis, spinal hyperpathia, vestibular abnormalities, ataxia, paraparesis, weight loss, anorexia, uveitis, lameness, renal failure, and respiratory distress.
   - Common clinicopathologic features are leukocytosis, hyperglobulinemia, azotemia, and hypercalcemia are.
   - Granulomatous inflammation in multiple organs, including bone, kidney, and spleen, is frequently observed.
- The disease can generally be diagnosed based on clinical, radiographic, and pathological findings.
Cases recently reported:

1. Diagnostic value of MRI in dogs with inflammatory nasal disease. 363
2. What causes canine sino-nasal aspergillosis? A molecular approach to species identification. 364
3. Spontaneous pneumothorax associated with Aspergillus bronchopneumonia in a dog. 365
4. Cytokine and transcription factor expression by Aspergillus fumigatus-stimulated peripheral blood mononuclear cells in dogs with sino-nasal aspergillosis. 366
5. A novel case of canine disseminated aspergillosis following mating. 367
6. Sinonasal aspergillosis in dogs: a review. 368
7. Toll- and NOD-like receptor mRNA expression in canine sino-nasal aspergillosis and idiopathic lymphoplasmacytic rhinitis. 369
8. Clotrimazole and enilconazole distribution within the frontal sinuses and nasal cavity of nine dogs with sinonasalaspergillosis. 370
10. Disseminated aspergillosis in a dog due to Aspergillus alabamensis. 372
11. Sensitivity and specificity of a blood and urine galactomannan antigen assay for diagnosis of systemic aspergillosis in dogs. 373
12. A novel case of canine disseminated aspergillosis following mating. 374
13. Aspergillus fumigatus bronchopneumonia in a Hellenic shepherd dog. 375
14. Cavitating pulmonary lesions in German shepherd dogs. 376
15. Clinical resolution of nasal aspergillosis following therapy with a homeopathic remedy in a dog. 377
16. Aspergillus versicolor, a new causative agent of canine disseminated aspergillosis. 378
17. Frontal sinus depth at four landmarks in breeds of dog typically affected by sinonasal aspergillosis. 379
18. Aspergillus fumigatus Bronchopneumonia in a Hellenic Shepherd Dog. 380
19. Acute phase protein concentrations in dogs with nasal disease. 381
20. Long term survival in two German shepherd dogs with Aspergillus-associated cavitary pulmonary lesions. 382
21. Otomycosis due to Aspergillus spp. in a dog: case report and literature review. 383
22. Efficacy of intrasinusal administration of bifonazole cream alone or in combination with enilconazole irrigation in canine sino-nasal aspergillosis: 17 cases. 384
23. Chronic monolateral otomycosis in a dog caused by Aspergillus ochraceus. 385
24. Repeated rhinoscopic and serologic assessment of the effectiveness of intranasally administered clotrimazole for the treatment of nasal aspergillosis in dogs. 386
6.2. Aspergillosis in cats

Feline aspergillosis includes

- Sinonasal aspergillosis (SNA) can be invasive or noninvasive and is most commonly caused by Aspergillus fumigatus and Aspergillus niger. SNA has a favorable prognosis with treatment.

- Sino orbital aspergillosis (SOA) is an invasive mycosis that is being increasingly recognized, and is most commonly caused by a recently discovered pathogen Aspergillus felis. The prognosis for SOA remains poor.

Veterinary images, Nasal, sinus and orbital aspergillosis in a cat.
Severe bone erosion rostrally through the nasal bone.

Martin L. Whitehead, & Peter W. Kettlewell,. Chipping Norton Veterinary Hospital, Chipping Norton, Oxon

Cases recently reported:

1. Aspergillosis in cats: ABCD guidelines on prevention and management. 389
2. Aspergillus felis sp. nov., an emerging agent of invasive aspergillosis in humans, cats, and dogs. 390
3. Feline aspergillosis. 391
4. Otomyositis due to Aspergillus spp. in a dog: case report and literature review. 392
5. Chronic monolateral otomyositis in a dog caused by Aspergillus ochraceus. 393
6. Invasive mould infections of the naso-orbital region of cats: a case involving Aspergillus fumigatus and an aetiological review. 394
7. Intranasal infusion of clotrimazole for the treatment of nasoaspergillosis in two cats. 395
8. Bilateral orbital and nasal aspergillosis in a cat. 396.
9. Computed tomographic findings of fungal rhinitis and sinusitis in cats. 397
10. Aspergillus flavus keratomyositis in a cat treated with topical 1% voriconazole solution. 398
11. Isolation of Aspergillus udagawae from a fatal case of feline orbitalaspergillosis. 399
12. Feline sino-orbital aspergillosis: an emerging clinical syndrome. 400
13. Use of posaconazole in the management of invasive orbitalaspergillosis in a cat. 401
6.3. Aspergillosis in horses

Aspergillosis in horses is a fungal disease caused by *Aspergillus spp.* *Aspergillus spp.* are very common in the environment, especially in moldy feed and bedding. They are opportunistic pathogens and often cause disease in horses that are immunosuppressed from debilitating conditions (e.g., enterocolitis, septicemia, neoplasia, Cushing's disease, equine protozoal myeloencephalitis) or major surgery or that have been treated with immunosuppressive drugs. They can infect internal organs, most commonly affects the guttural pouches but infection may also lead to abortion, keratomycosis, rhinitis and rarely pulmonary aspergillosis.

1. Equine Aspergillus Rhinitis, Pulmonary Aspergillosis

   **Historical**

   - Rivolta (1856) recorded the first case of aspergillosis in horses, but was frequently restricted to infection of the nasal sinuses and the guttural pouches. In a case described
   - Thary and Lucet (1895) described a rapidly developed rapidly disease that showed generalized interstitial haemorrhage with caseous nodules in the kidneys in a four-year-old mare.
   - Foulerton (1899) described the lung of a horse with typical aspergillotic nodules
   - Noller & Krause in 1924, and Tscherniak (1928) gave details of several more cases Romanov (1928) reported meningeal involvement.

Infection is by inhalation of an overwhelming number of spores or by translocation of organisms across an inflamed gastrointestinal tract. Aspergillus pneumonia is almost uniformly fatal, often with no or mild respiratory signs. The two forms of Aspergillus pneumonia probably reflect the two portals of entry, with fungal proliferation and invasion of the small airways occurring secondary to inhalation, and angioinvasive aspergillosis with lesions centered around large blood vessels likely due to hematogenous infection originating from the gastrointestinal tract. In two retrospective studies of invasive pulmonary aspergillosis, 41 of 49 cases were associated with enterocolitis.

Pulmonary aspergillosis is characterized grossly by multiple nodules throughout the lungs. On histologic examination, there is often necrosis and purulent inflammation. Necrosis is due to toxin and enzyme production as well as vascular obstruction. Fungal invasion of blood vessels is common and results in vasculitis, thrombosis, infarction, and necrosis. Chronic lesions are granulomatous, with macrophages, neutrophils, and multinucleated giant cells predominating.
2. Guttural Pouch Aspergillosis

Aspergillosis most often affects the guttural pouch. The infected guttural pouch is characterized by a necrotizing inflammation and is thickened, haemorrhagic, and covered by a friable pseudomembrane. There is no age, sex or breed predisposition for guttural pouch mycosis and both left and right pouches are affected with equal frequency.

Guttural pouch mycosis is characterised by spontaneous epistaxis (often in a resting horse) as a result of fungal erosion of the internal carotid artery. Other clinical signs include nasal discharge and dysphagia. Mycotic plaques are usually located on the caudodorsal aspect of the medial guttural pouch. In some instances, fungal plaques may be multiple or diffuse.
Recently reported cases:

1. A Case of Equine Aspergillosis: A Novel Sampling Procedure for Diagnosis. 402
2. Guttural pouch mycosis in six horses in New Zealand 403
3. *Aspergillus fumigatus* guttural pouch mycosis in a horse which died from acute pulmonary oedema. 404
4. Guttural pouch mycosis in a donkey (*Equus asinus*): a case report. 405
5. Guttural pouch mycosis in a 6-month-old filly. 406
6. Diagnosis and management of guttural pouch mycosis. 407
7. Atypical guttural pouch mycosis in three horses. 408

6.4. *Aspergillosis in cattle*

*Aspergillus* *spp* are a group of soil mould which are an aerosol cause of mycotic abortion, respiratory diseases and aflatoxicosis in cattle worldwide. Species of *Aspergillus* which are pathogenic to cattle include:

- *Aspergillus fumigatus*
- *Aspergillus terreus*
- *Aspergillus flavus*

In affected cattle, infections with *Aspergillus* may be asymptomatic. In respiratory aspergillosis, respiratory symptoms such as coughing, dyspnea and hemoptysis may be apparent. In some cattle, this can be rapidly fatal as dissemination of spores occurs through the pulmonary circulation.

Mycotic placentitis, also caused by *Aspergillus* *spp*, is usually a sporadic cause of abortion affecting a small percentage of cattle in a herd. Cattle housed in the winter can experience an abortion rate of up to 30% due to mycotic placentitis, if feed or bedding is heavily contaminated with molds. Ingested mold is thought to localize in the cows' intestinal tract and then spread to the placenta through the blood. High rates of mycotic placentitis have also been correlated with heavy rainfall during the haymaking season, episodes of subclinical grain overload and with prolonged intensive antibiotic treatment.

On postmortem, affect lungs contain multiple discrete granulomas, and the disease grossly resembles tuberculosis.

Aspergillosis has a number of clinical manifestations in the cow including mastitis, placentitis, diarrhoea, ocular infection and mycotic pneumonia. Abortion in the second or third trimester of pregnancy has also been described.

- In the case of pulmonic disease, clinical signs may include pyrexia, cough, dyspnoea and tachypnoea but may be limited to vague signs such as weight loss or signs of mild respiratory disease.
- In aborting cattle, the foetus and placenta are retained and foetal lesions such as bronchopneumonia and dermatitis may be seen.
- Mastitic cows may display depression, weight loss and pyrexia with purulent mammary secretions and a hot, swollen udder.
Recently reported cases:

1. Involvement of fungal species in bovine mastitis in and around. 409
2. Application of real-time PCR for detection of Aspergillus species in aborted ruminant foetuses. 410
3. Mycotic abortion in cattle. 411
4. Abortus by *Aspergillus fumigatus* and *A. niger* in cattle in southern Brazil. 412
5. Mastitis by Aspergillus fumigatus in sheep. 413
6. [Mycotic placentitis in cattle]. 414
8. Aspergillus nidulans and Aspergillus fumigatus as causal agents of bovine mastitis. 416
9. Cases of Aspergillus mastitis in cattle. 417
10. Caprine mastitis due to aspergillosis and zygomycosis: a pathological and immunohistochemical study 418

6.5. Aspergillosis in Sheep and goats

There have been only five reports of aspergillosis in sheep. The lesions in lambs consist of small (2-3 mm. Diam.) bluish-grey nodules surrounded by a narrow haemorrhagic zone, and closely resemble those caused by the lungworm *Muellerius capillaris* (Andersen 1927). The most recent report of the disease is in the Annual Report of the New Zealand Department of Agriculture for 1955.

Van Hellens (1902-03) investigated in Finland one of the few epidemics of aspergillosis on record among sheep. The animals were adult and showed chronic bronchitis and catarrhal pneumonia closely resembling the symptoms of tuberculosis. Death occurred up to one year after the appearance of symptoms. Conidiophores of *A. fumigatus* were found in the sputum of affected sheep and numerous discrete and sometimes well calcified nodules 1-7 mm. in diam. were present in the lungs. Nobel & Shamir (1956) described a rather different condition in which granulomatous lesions containing the hyphae of *A. fumigatus* were found in the lungs of a day-old lamb, and they considered the infection had taken place *in utero*.

Recently, two cases of systemic aspergillosis were described by Pérez, 1999, in dairy sheep from a flock in which fungal mastitis appeared subsequent to the antibiotic treatment of animals before parturition. Lesions characterized by necrosis and a pyogranulomatous exudate were observed in the mammary glands, supramammary and mediastinal lymph nodes, kidneys, lung, liver, heart, forestomachs and brain. The intense vasculitis with thrombosis observed in various organs, but especially in the mammary glands, suggested a haematogenous dissemination of the infection from this organ. The aetiological diagnosis was accomplished by the immunohistochemical staining of the fungal structures seen in the histological sections by the specific Aspergillus monoclonal antibody Mab-WF-AF-1 together with the isolation of Aspergillus fumigatus in pure culture from affected tissues.
In goats, nasal and cutaneous aspergillosis was reported by do Carmo et al., 2014. The clinical signs were severe respiratory distress due to partial nasal obstruction, bilateral mucopurulent nasal discharge, skin nodules on the ears and dorsal nasal region and focal depigmentation of the ventral commissure of the right nostril. At necropsy examination, sagittal sectioning of the head revealed a yellow irregular mass extending from the nasal vestibule to the frontal portion of the nasal cavity. Microscopically, there was pyogranulomatous rhinitis and dermatitis, with numerous intralesional periodic acid–Schiff-positive fungal hyphae morphologically suggestive of *Aspergillus* spp. *Aspergillus niger* was isolated by microbiological examination.

**Experimental aspergillosis in sheep and goats**

**Mycotic abortion** was induced in pregnant ewes and goats by El-Naggar et al. (1997). Twelve animals were inoculated i.v. with 10 ml of *A. fumigatus* suspension containing $2 \times 10^7$ viable spores/ml and 5 pregnant animals were kept as control. All experimental animals aborted between 19-30 days post inoculation. Uteri, maternal and fetal placenta and fetal tissues showed extensive necrosis, infarction and invasion with *A. fumigatus* hyphae. Histological examination revealed mycotic granulomatous inflammation in the lungs, heart, brain, spleen and kidneys.
Lung of aborted ewe showing large granulomatous mycotic abscess and multiple hyphae of *A. fumigatus* (PAS).

Left: Lung of aborted ewe showing typical dichotomous branching septated hyphae with reproductive vesicles (GMSX400). Right: Lung of aborted ewe showing nodules of *A. fumigatus*.

Left: Spleen of aborted ewe showing the arrangement of hyphae of *A. fumigatus* within tissue (H&E), right: mycotic granuloma with *A. fumigatus*.

Placenta of aborted goat showing areas of coagulative necrosis (left) and *A. fumigatus* hyphae (right).
Experimental *Aspergillus fumigatus* mastitis in 4 goats and 4 ewes was induced by El-Naggar et al. (1997). The left halves of the udders were inoculated intramammary with 2 ml of viable *A. fumigatus* spore suspension (1.65×10⁸ spores /ml). The right halves were inoculated with the diluent. After 25 days the animal were sacrificed and examined. All animals showed granulomatous inflammation of the udder. *A. fumigatus* was seen in the center of the lesion, which was heavily infiltrated with neutrophils, macrophages and surrounded by fibrous connective tissues. Diffuse necrosis and cavitation of the udder tissues were detected and vesicles of *Aspergillus fumigatus* were also seen.
Cases recently reported:

1. Nasal and Cutaneous Aspergillosis in a Goat
2. Generalized aspergillosis in dairy sheep.
3. Caprine mastitis due to aspergillosis and zygomycosis A pathological and immunohistochemical study.

6.6. Aspergillosis in pigs

Records of aspergillosis in pigs are also rare. Berg (1898-99) first described the disease as a persistent cough associated with a lobar pneumonia and nodule formation. The spleen and kidney were enlarged and congested, and nodular lesions were found in the mesenteric lymph nodes. Berg did not obtain any isolates from the lesions but assumed that an *Aspergillus* was the cause of the disease. Generalized infection in a pig was also reported by Nuvoletti & Casella (1903).

![Aspergillus fumigatus infection of the lung in piglets, www.aspergillus.org.uk](www.aspergillus.org.uk)

6.7. Aspergillosis in camels

El-Khouly et al. (1992) reported on death in racing camels (Camelus dromedarius) associated with a specific disease syndrome. Clinical signs included pyrexia, coughing, lachrymation, oedema of the throat and submandibular region and enlargement of submandibular lymph nodes. In terminal cases nervous signs were present and sometimes there was bloody diarrhoea and vomiting. Of 480 camels at least 70 animals were affected with the disease and about 40 died. Morbidity and mortality was greater in camels recently imported. Consistent necropsy findings were extensive petechial and ecchymotic haemorrhage beneath the epicardium, endocardium and visceral pleura and in the mediastinal lymph nodes, and haemorrhagic oedema.
of the pharyngeal and laryngeal areas. Haemorrhages occurred more variably in abdominal organs and on the omasal and abomasal mucosa. Bronchopneumonia, omasitis and abomasitis were observed on microscopic examination, together with liver and kidney lesions of presumed toxic origin. Fungal hyphae and, occasionally, the characteristic conidial morphology of Aspergillus fumigatus were seen in sections and direct smears from lesions in the respiratory and alimentary tracts. A fumigatus was cultured from trachea, bronchi, bronchioles, lung tissue, heart blood, omasum, abomasum, ileum and submandibular lymph nodes. Whether the role of Aspergillus in the overall syndrome is primary or secondary has not been established; no other potential aetiological agent has been identified.

Dehkordi et al. (2012) performed research for detection of Aspergillus species (A. fumigatus, A. flavus, A. niger and A. terreus) in aborted bovine, ovine, caprine and camel foetuses by real-time PCR in Iran. After modification of real-time PCR on abomasal contents, from the total number of 970 samples, 141 (14.53%) gave positive results for Aspergillus species. Of them, 62 (17.71%), 33 (14.04%), 27 (12.05%) and 19 (11.8%) positive specimens were detected in bovine, ovine, caprine and camel foetuses respectively. Statistical analysis showed significant differences (P<0.05) between bovine and camel and bovine and caprine aborted foetuses. Aspergillus abortion was the most prevalent in cattle whereas camels tended to be the most resistant.

An invasive form of aspergillosis in an alpaca (Lama pacos) was described, with dissemination causing small abscesses and multifocal areas of necrosis in the lung, heart, spleen and kidneys. Histological sections showed hyphae morphologically compatible with an Aspergillus species. Direct immunofluorescent testing confirmed the diagnosis of aspergillosis.( Severo et al., 1989).

**6.8. Aspergillosis in American bison**

Rewell & Ainsworth (1947) showed how the respiratory passages of an American bison at the London zoo were found on post-mortem examination to be lined with a greenish felt of A.fumigatus with absence of severe lung lesions.

de los Moneros et al. (1999) reported on concomitant nasal zygomycosis and pulmonary aspergillosis in a 3-mo-old female American bison calf (Bison bison) in Pennsylvania (USA). Etiologic diagnosis was made by immunohistochemistry using a panel of monoclonal antibodies and heterologously absorbed polyclonal antibodies. In the lungs fungal infection was accompanied by hemorrhage, fibrin exudation, and infiltration with neutrophils. Fungi were observed to penetrate apparently normal epithelial lining of the nasal turbinates, and there was hemorrhage, edema, and invasion of blood vessels in the submucosa. In vessels fungi were typically associated with thrombosis. The calf may have been infected due to a high level of exposure to mouldy feed and litter in the environment in combination with a collapse of it's natural defence mechanisms.
6.9. Aspergillosis in monkeys

Scott (1930) gave details of nine cases of mycosis (aspergillosis?) and a further nine associated with tuberculosis in captive monkeys encountered at the London zoo. The lungs were the chief organs involved but miliary nodules were occasionally found throughout the viscera.

Jurczynski (2012) reported on invasive aspergillosis in a putty-nosed monkey (Cercopithecus nictitans) with adrenocortical Cushing's syndrome. An 18-year-old captive female putty-nosed monkey (Cercopithecus nictitans) with a history of long-term infertility and hyperglucocorticism was euthanized because of perforating thoracic trauma induced by group members and subsequent development of neurological signs.

Complete necropsy and histopathological examination of formalin-fixed tissue samples was carried out. The monkey showed invasive pulmonary and cerebral infection with Aspergillus fumigatus together with adrenocortical neoplasia and signs of Cushing’s syndrome, such as alopecia with atrophic skin changes, evidence for diabetes mellitus and marked immunosuppression.

6.10. Aspergillosis in deers

Outbreaks of pulmonary aspergillosis have been reported in hares in Sweden (Thjostta, 1933; Hölfers & Lilleengen, 1947) and also in roe-deer in that country and Switzerland, in which the conchal and ethmoid bones as well as the lungs and other organs became affected by tumour-like growths containing hyphae (Krembs, 1937; Burgisser, 1955). When specific determination had been carried out, A. fumigatus was the most frequent isolate but Burgeon (1929) reported A. niger from nodular lesions in the lungs of a bull, a heifer and a stag in Indo-China.
During 1988, pulmonary mycosis was diagnosed in four of 116 farmed deer examined on suspicion of tuberculosis. The histopathology showed allergic bronchopulmonary mycosis in a red deer (Cervus elaphus) and the agent was identified as a zygomycete, probably Absidia corymbifera, by immunofluorescence staining. Three fallow deer (Dama dama) had invasive necrotizing mycotic pneumonia and progressive exudative mycotic alveolitis caused by Aspergillus fumigatus. In the red deer, weakness due to paratuberculosis had probably promoted the mycotic infection. The three fallow deer were bred on another farm, where predisposing factors included mouldy straw and incorrect management. (Jensen et al., 1989)

![Aspergillus pneumonia in lung of deer © Bristol Biomedical Image Archive. pathmicro.med.sc.edu](image)

6.11. Aspergillosis in rabbits

Aspergillosis in domestic rabbits has been reported by Schöppler (1919) and Höppli (1923). Patton (1975) described cutaneous and pulmonary aspergillosis in rabbits.
6.12. Aspergillosis in guinea-pigs

Ainsworth & Austwick (1955a) have recorded the disease in guinea-pigs. Recently, guinea-pigs are used for assessment of Aspergillus fumigatus burden in pulmonary tissue of antimycotics.

4.13. Aspergillosis in lesser blind mole rats

Tamam and Refai (2013) reported on seven wild Egyptian lesser blind mole rat (*Spalax leucodon* Egyptianus) that died naturally in the wild. All the animals had large pulmonary lesions that on microscopic, microbiological, and ultrastructural analysis were shown to contain mixed infections with *Alternaria alternata* and *Aspergillus candidus*. Some of the lesions were circumscribed with fibroblastic proliferation and inflammatory response. The lungs had haemorrhage and chronic inflammatory response to the organisms, which is likely to have been the cause of death.

(A) Thoracic cavity of *Spalax leucodon* showing large, tumour-like lesions replacing the apical left lung lobe and large, firm brown lesions in the caudal and right lobes (yellow arrows). (B) Thoracic cavity containing brown, consolidating focal lesions in the centre of the left lung lobe, emphysematous change (red arrows), and red hepatisation of the lower right lobe (violet arrow).

Reidarson et al. (1998) reported on a 4-yr-old male bottlenose dolphin (Tursiops truncatus) that developed an Aspergillus fumigatus pneumonia. Fungal elements were identified by cytology and microbiology from endoscopic bronchoalveolar lavage and brushings of a raised yellow endobronchial lesion. The results of qualitative immunodiffusion serology, a technique that identifies specific circulating antibodies to Aspergillus fumigatus, were suggestive of an active infection. The dolphin was treated with itraconazole for over 2 yr, which resulted in remission of clinical signs. Pneumonia caused by Aspergillus sp. accounts for the large majority of pulmonary mycoses in marine mammals.

The clinical history, laboratory data, and gross and histological findings are described and discussed by Brian et al. (2005) for three cases of fatal pulmonary aspergillosis in three species of dolphins.

Reported cases

1. Invasive aspergillosis in a Putty-nosed monkey (Cercopithecus nictitans) with adrenocortical Cushing’s syndrome. 422
2. Aspergillosis in camels affected with a specific respiratory and enteric syndrome. 423
3. Pulmonary mycosis in farmed deer: allergic zygomycosis and invasive aspergillosis. 424
4. Application of real-time PCR for detection of Aspergillus species in aborted ruminant foetuses. 425
5. Efficacy of voriconazole against invasive pulmonary aspergillosis in a guinea-pig model. 426
6. Experimental aspergillosis in guinea pigs: influence of itraconazole on fungaemia and invasive fungal growth. 427
7. Occurrence of Aspergillus fumigatus Fresen. in the Lung of an American Bison. 428
8. Nasal zygomycosis and pulmonary aspergillosis in an American bison. 429
10. Invasive aspergillosis in an alpaca (Lama pacos). 431
11. Pulmonary aspergillosis in three species of dolphin. 432
12. Cutaneous and pulmonary aspergillosis in rabbits. 433
13. Dual mycotic pulmonary granulomas caused by Alternaria alternata and Aspergillus candidus in the wild egyptian mole rat (Spalax leucodon egyptiacus). 434
7. Aspergillosis in birds

- Aspergillosis was first described in a wild duck in 1833 and in turkeys as early as 1898. All species of birds probably are susceptible.
- *Aspergillus fumigatus* is a common cause of the disease. However, other species like *A. flavus*, *A. niger*, *A. nidulans*, and *A. terreus* may also be isolated from avian cases of aspergillosis (sometimes in mixed infections) but much less frequently than *A. fumigatus*.
- The bird comes in contact with the organisms through contaminated feed, litter or premises. The disease is not contagious and does not spread from one bird to another. Most healthy birds can withstand repeated exposure to these organisms. Inhalation of large amounts of the infectious form of the mould or reduced resistance of the bird apparently results in infection.

7. 1. Aspergillosis in poultry

Infection by *Aspergillus* sp. has been reported in almost all domesticated avian species and production types: layer cockerels, pullets in cages, broiler breeders, and growers of chicken or turkey poults, duck breeders and goslings. Aspergillosis is a disease, usually of the respiratory system, of chickens, turkeys, and less frequently ducklings, pigeons and geese. In chickens and turkeys, the disease may be endemic on some farms.

- *Aspergillus fumigatus* can penetrate egg shells under ideal growth conditions and thus infect the embryos. Such eggs will often appear green when candled (the embryo will be dead). Infected embryos may hatch with well-developed lesions.
- If infected eggs break in the hatchery, large numbers of spores are released which contaminate the hatchery environment and air systems can lead to severe outbreaks in very young birds (less than 3 weeks of age). Eggs punctured for in-ovo injection are particularly susceptible to contamination. Even low-level contamination of hatching or air systems can result in mortalities of 50% or greater when in-ovo injection is used.
- High mortality rates are seen in newly hatched chicks and poults that inhale large numbers of spores during hatching in contaminated incubators. The diseased is called brooder pneumonia. In older birds, infection is caused primarily by inhalation of spore laden dust from contaminated litter or feed or dusty range areas.
- Dyspnea, hyperpnea, somnolence and other signs of nervous system involvement, inappetence, emaciation, and increased thirst may be seen. In chicks or poults up to 6 weeks, the lungs are most frequently involved.
- Airsacculitis in young mature turkeys is a leading cause of postmortem condemnation. Pulmonary lesions are characterized by cream-coloured plaques a few mm to several cm
in diameter; occasionally, mycelial masses may be seen within the air passages on gross examination. The plaques also may be found in the syrinx, air sacs, liver, intestines, and occasionally the brain. The encephalitic form is most common in turkeys. An ocular form, in which large plaques has been seen in chickens and turkeys.
7.2. Aspergillosis in wild birds:

*A. fumigatus* has been isolated from lesions in wild birds since the early 1800s. Major die-offs of free-ranging wild birds have been reported from waterfowl, gulls, and corvids following dumping of mouldy waste grains in areas where birds feed. Aspergillosis has also been reported in penguins, raptors, migratory waterfowl, psittacines and zoologic specimens, such as flamingos.

7.2.1. Aspergillosis in penguins

On Sunday, November 10th, 2013, staff at the Calgary Zoo made the difficult decision to euthanize a 14-year-old male Gentoo penguin Houdini. He had been sick for almost a month.
The results of a necropsy confirmed severe aspergillosis – a fungal infection that affects the respiratory system and is one of the most common causes of death in captive penguins and has been recorded in wild penguins. Penguins are among several birds that are exquisitely sensitive to acquiring the infection, with increased disease noted when the spore levels become concentrated and/or the birds immune systems are depressed as when they moult.

The necropsy of penguin showed that airsacs were diffusely thickened, opaque, and studded with multiple off-white to pale green dull. Similar plaques were scattered across coelomic viscera serosal surfaces and adherent to the lungs which were diffusely dark red purple and wet. The histopathology revealed that granulomatous, heterophilic, and necrotizing inflammation with myriad intralesional fungal hyphae morphologically consistent with *Aspergillus* spp. were present in the lungs, airsacs, kidneys, oviduct, trachea, mesentery, and serosal surfaces of coelomic viscera. There was significant atrophy of adipose tissue, skeletal muscle, liver, and pancreas.

In a retrospective studies in Gifo University, Yanai reported that, 10 of 42(28.3%) cases of death in penguins in Japan were due to aspergillosis.
7.2.2. Aspergillosis in parrots

Aspergillosis is less common in companion parrots; however, disease is more prevalent in African grey parrots (*Psittacus erithacus*), Amazon parrots (*Amazona* spp.), Pionus parrots (*Pionus* spp.) and macaws. The likelihood of a fungal infection is increased if the bird is housed in an environment in which there is poor sanitation, high relative humidity and high temperatures, which can increase the load of fungal spores. A bird with a weakened immune system due to steroid administration or concurrent illness (particularly when treatment involves long-term antibiotics) is also at greater risk for aspergillosis.

- Like humans, parrots and other large birds cough when they experience a respiratory irritation. Coughing can be normal when it only occurs every now and then, but when parrot's cough
becomes chronic, it could be a sign of aspergillosis. Spores released by the aspergillus can get trapped in the bird's respiratory system, causing the cough.

- In addition to coughing, when aspergillus spores get into parrot's throat and lungs its voice may change and it may refuse to talk entirely.

- Spores released by aspergillus affect different parts of the respiratory system in different ways. Such symptoms include labored breathing or sudden fits of suffocation. Your bird's neck may turn blue as it tries to talk or cough. This is indicative of choking, but the bird could also be suffocating on an aspergillus spore. In some instances, parrots are known to suddenly drop dead after inhaling an aspergillus spore.

7.2.3. Aspergillosis in quails

Aspergillosis in quail is characterized by the formation of yellowish white nodular growth in lungs and intercostal areas with thickened air sacs. Histopathologically, lungs show severe congestion with focal haemorrhages, multiple granulomatous inflammation with caesative necrotic areas in centre. Various fungal elements like conidia, long septate hyphae with mononuclear and heterophilic infiltration are seen in these areas. Microbiological study reveals velvety bluish green colony of Aspergillus fumigatus.

Nodules in the air sacs and on the peritoneal serosa in a case of aspergillosis in a common quail.
www.fmv.utl.
7.2.4. Aspergillosis in ostrich

Aspergillosis in ostrich was reported by Perelman and Kuttin (1992), Katz *et al.* (1966), Pérez, *et al.* (2003) Yokota *et al.* (2004), SANCAK A.A. and PARACIKOLU (2005), Khosravi (2008), Shathele et al. (2009) and Tijani *et al.* (2012). ARAGHI *et al.* (20014) describes an aspergillosis outbreaks in ostrich flocks of eastern Iran during 2010–2012. They reported that signs of respiratory involvement, anorexia, depression, progressive emaciation and decreased production were the most commonly seen in affected farms. Morbidity rate was 43% and 54.53% in breeding birds and chickens, respectively. *Aspergillus fumigatus* and *Aspergillus niger* were identified.
7.2.5. Aspergillosis in red-tailed hawk (*Buteo jamaicensis*).

Aspergillosis in red-tailed hawk       Multiple granulomas in the lungs       *A. fumigatus* colony with spores in air sacs, MVS

7.2.6. Aspergillosis in Red-billed Toucan (Yanai, Gifu Univ)

Aspergillosis in Red-billed Toucan, Yanai, Gifu Univ.: multifocal lesions in the lung and liver

Hyphae radiating from a central necrotic nodule

Conidia heads of *Aspergillus* in a pulmonary cavity
7.2.7. Aspergillosis in Snow Owl (Yanai, Gifu)

Severely thickened air sacs of Snow Owl caused by A. fumigatus, Yanai, Gifu

7.2.8. Aspergillosis in Goshawk

Aspergillosis in Goshawk, Yanai, Gifu
7.2.9. **Aspergillosis in Cormorants**

Aspergillosis in Cormorants, multifocal necrosis with Aspergillus hyphae in the lung

7.2.10. **Aspergillosis in swans**

Souza *et al.* (2005) reported on mortality in wild swans in Northwest Washington State due to aspergillosis.

Abou-Rawash *et al.* (2008) reported on disseminated aspergillosis in a Whooper Swan (Cygnus Cygnus) in Japan. A Whooper Swan which usually migrates from Siberia to the north of Japan in the winter season was found in Kume Island at the south of Japan in a state of pronounced illness. Blood and serum analysis revealed hypoalbuminaemia elevated serum level of uric acid (UA) and creatinin phosphokinase (CPK). The bird succumbed after unsuccessful attempts for treatment. At necropsy, the bird had multiple focal and coalescent caseated granulomatous nodules of whitish greenish color on the thoracic and abdominal air sacs, the lungs, and the serosal surfaces of the spleen, liver and kidneys. At the inner side of the air sacs hyphal growth with dark greenish color were scattered on most of the surface. Histopathologically, the present case had a sever degree of chronic disseminated aspergillosis. The granulomas had a central necrotic areas consisted of necrotic cell debris and hyphae with the microscopical features of Aspergillus. A. fumigatus was identified in tissues by PAS, GMS, and immunohistochemically. PCR was very successful to identify the causative fungus like other infectious agent.

On Jan. 27, 2014, 149 dead swans have been found in Whatcom County. The death was attributed also here to aspergillosis. a disease which is being blamed for the deaths of trumpeter swans spending the winter on Whatcom County's Wiser Lake.
7.2.11. Aspergillosis in kiwi

The Wellington Zoo reported on 30 September 2013 that, eight young rowi—the rarest species of kiwi—have died from respiratory tract infections. The kiwi were being treated for nematodes (a type of worm) in Wellington Zoo when they started to show signs of respiratory problems. The respiratory tract infection was caused by the fungus *Aspergillus spp.* which is commonly found in the environment. It is thought that the birds’ weakened immunity from the nematodes made them susceptible to this. Travis *et al.* (2014) reported on Isolation and Identification of *Aspergillus* spp. from Brown Kiwi (*Apteryx mantelli*) Nocturnal Houses in New Zealand.
Eight Kiwi chicks have died from respiratory tract infections at Wellington Zoo.

Recently reported cases:

1. Secondary Aspergillus fumigatus infection associated with coloidal goiter in a black-masked lovebird (Agapornis personata). 435
2. Drug resistance of Aspergillus fumigatus strains isolated from flocks of domestic geese in Poland. 436
3. Isolation and identification of Aspergillus spp. from brown kiwi (Apteryx mantelli) nocturnal houses in New Zealand. 437
4. Monitoring of fungal loads in seabird rehabilitation centers with comparisons to natural seabird environments in northern California. 438
5. Mutations in the Cyp51A gene and susceptibility to itraconazole in Aspergillus fumigatus isolated from avian farms in France and China. 439
6. Environmental contamination by Aspergillus spp. in laying hen farms and associated health risks for farm workers. 440
7. Isolation and identification of Aspergillus spp. from brown kiwi (Apteryx mantelli) nocturnal houses in New Zealand. 441
8. [Radiograph ic findings in raptors affected with a mycosis of the respiratory tract]. 442
9. A model for treating avian aspergillosis: serum and lung tissue kinetics for Japanese quail (Coturnix japonica) following single and multiple aerosol exposures of a nanoparticulate itraconazole suspension. 443

10. Inflammatory marker profiles in an avian experimental model of aspergillosis. 444
11. Opportunistic infection of Aspergillus and bacteria in captive Cape vultures (Gyps coprotheres). 445
12. Emerging and reemerging diseases of avian wildlife. 446
13. Assessment of Aspergillus fumigatus pathogenicity in aerosol-challenged chickens (Gallus gallus) belonging to two lineages. 447
15. . The occurrence of aspergillosis in flock of turkey poult. 449
16. Serum protein electrophoresis by using high-resolution agarose gel in clinically healthy and Aspergillus species-infected falcons. 450
17. Innate Immunity and the Role of Epithelial Barrier During Aspergillus fumigatus Infection. 451
18. A longitudinal study on the incidence of mortality of infectious diseases of commercial layer birds in Bangladesh. 452.
19. Aspergillus fumigatus and other thermophilic fungi in nests of wetland birds. 453
20. Microsatellite typing of Aspergillus flavus from clinical and environmental avian isolates.  
22. *Aspergillus fumigatus* from normal and condemned carcasses with airsacculitis in commercial poultry.  
24. Serologic testing for aspergillosis in commercial broiler chickens and turkeys.  
25. Aspergillosis in gamebirds and ducks.  
27. Aspergillosis in gamebirds and ducks.  
28. Spinal aspergillosis in pheasants.  
31. Diagnosis and Treatment of Aspergillosis in An Ostrich Flock.  
32. Microsatellite typing of avian clinical and environmental isolates of *Aspergillus fumigatus*.  
34. Molecular epidemiology and virulence assessment of *Aspergillus fumigatus* isolates from white stork chicks and their environment.  
35. *Aspergillus* infections in birds: a review.  
36. Embryonated eggs as an alternative infection model to investigate *Aspergillus fumigatus* virulence.  
37. Pyogranulomatous Aspergillosis in An Endemic Formosan Blue Magpie.  
38. Aspergillosis in turkey poult's.  
39. Clinical, mycological and pathological findings in turkeys experimentally infected by *Aspergillus fumigatus*.  
40. Efficacy of voriconazole in Japanese quail (*Coturnix japonica*) experimentally infected with *Aspergillus fumigatus*.  
42. Aspergillosis in ostriches.  
43. Aspergillosis and gastric impaction in an ostrich.  
44. *Aspergillus fumigatus* infection in an ostrich (*Struthio camelus*).  
45. Outbreak of severe disseminated aspergillosis in a flock of ostrich (*Struthio camelus*).  
46. Fatal Aspergillosis in an Ostrich (*Struthio camelus*) Predisposed by Pulmonary Haemangioma in the Kingdom of Saudi Arabia.  
48. Outbreak of aspergillosis in a flock of adult ostriches (*Struthio camelus*).  
50. Disseminated aspergillosis in a Whooper Swan (*Cygnus Cygnus*).
8. Laboratory diagnosis of aspergillosis

8.1. Direct microscopic examination

8.1.1. Wet preparations

One of the simplest approaches to diagnose invasive aspergillosis is to examine appropriate specimens microscopically. Samples are prepared as wet preparation in potassium hydroxide solution and examined unstained for fungal hyphae.

8.1.2. Stained preparations

Preparations can be stained by various stains eg, Calcofluor white, Uvitex 2B, and Blankophor—which are water-soluble colourless dyes.
8.1.3. Histopathological examination

Histopathological examination of biopsy or autopsy material provides a diagnosis of proven invasive fungal infection (IFI). Tissue sections are stained by standard haematoxylin and eosin staining should reveal the presence of Aspergillus hyphae but stains such as period acid Schiff and Grocott’s silver should be carried out whenever a fungal infection is suspected. Aspergillus hyphae seen in tissue sections tend to be narrow (1–3 um in diameter) and septate.

![Image of Aspergillus hyphae in tissue sections](image1.jpg)

- Direct microscopic examination of corneal material by the method of Gram staining revealed the presence of fungal hyphae. Aspergillus keratitis: Histopathology of the biopsied mass showed a giant cell granuloma with surrounding numerous branching, septate hyphae. (H and E, x 40).
- Angioinvasion – Aspergillus hyphae invading a blood vessel, GMS stain, [www.stritch.luc.edu](http://www.stritch.luc.edu).
- Bronchoscopic biopsy demonstrated septate hyphae with branching at 45° (methenamine silver stain). [www.aspergillus.org.uk](http://www.aspergillus.org.uk)
8.1.4. Immunohistochemistry (IHC) or immunocytochemistry

Immunohistochemistry (IHC) or immunocytochemistry is a method for localizing specific antigens in tissues or cells based on antigen-antibodies recognition. Specificity should derive from binding of an antibody with its counterpart antigen at a light microscopic level. The use of an enzymatic label antibody such as horseradish peroxidase allows visualization of the labeled antibody using conventional light microscopy in the presence of a suitable chromogenic substrate system. IHC is now applied to routinely formalin-fixed paraffin-embedded tissues sections. Depending on the colorimetric developer, fungi stain dark brown or red, usually with a counterstain of hematoxylin. Immunohistochemical methods have the potential advantage of providing a rapid and specific identification of several fungi, allowing pathologists to identify unusual filamentous and yeast-like infections and accurately distinguish them from confounding artefacts.

Fixed tissue sections can be stained by immunohistochemical labelling using Aspergillus monoclonal antibody.


8.1.5. Molecular diagnosis in formalin fixed paraffin-embedded tissue

Two methods for extracting fungal DNA from paraffin wax embedded tissue sections, based on the TaKaRa DEXPAT™ kit and QIAamp® DNA mini kit, were optimised and compared by Paterson et al. (2003). DNA was amplified by PCR using pan-fungal probes, and detected by Southern blot hybridisation using a high stringency method with a probe specific for *Aspergillus fumigatus* and *A. flavus*.

Biwas et al. (2008) demonstrated *Aspergillus fumigatus* fungus by PCR-based RFLP technique from paraffin section of an eyeball of an eight-month-old child removed for endogenous endophthalmitis.
Sometimes a fungus is seen in a specimen or tissue and not cultured. It is important to identify such fungi to genus and preferably species level. Fresh non-embedded tissues have shown that sensitivity for PCR detection of fungi exceeds 95%, while the sensitivity of paraffin-embedded samples is currently ~60%. If fungal infection is strongly suspected prior to biopsy or resection, retention of some of the sample fresh (ie not placed in formalin) may facilitate aetiological diagnosis. Only for *Aspergillus* spp. is a commercially available technique to determine the genus of fungi found in tissue sections published, but this method does not separate species of *Aspergillus*. The majority of the published assays target specific rRNA genes (18S or D1-2 of 28S) or the intervening internal transcribed spacer (ITS1 and ITS2).

### 8.2. Isolation and identification

Most *Aspergillus* sp. grow relatively rapidly (typically within 48 hr) and on most microbiology media including both mycological media such as Sabouraud’s agar and blood agars used for general bacteriological culture. Identification of cultures of most species *Aspergillus* is generally straightforward by colony and microscopic morphology.
Aspergillus restrictus  Aspergillus candidus

Aspergillus niger  Aspergillus carbonarius

Aspergillus ustus  Aspergillus sydowii

A. versicolor  A. glaucus

Aspergillus equitis  Aspergillus hollandicus
Aspergillus terreus
Aspergillus flavipes
Aspergillus ochraceus
Aspergillus flavus
Aspergillus parasiticus
Aspergillus oryzae
Aspergillus wentii
Aspergillus fumigatus
Aspergillus felis

Aspergillus clavatus

Aspergillus nidulans

Aspergillus avenaceous

Aspergillus carneus,

Aspergillus giganteus

Aspergillus indologenus

Aspergillus deflectus
8.3. Molecular identification of aspergilli

Sequencing of genes, such as actin, calmodulin, ITS, rodlet A (rodA) and/or β-tubulin (βtub), has been used to distinguish *A. fumigatus* from related species. Multilocus sequence typing can alternatively be used for the identification of those related species, which is a strategy that also involves sequencing of several gene fragments. A few other techniques, such as random amplified polymorphic DNA, restriction fragment length polymorphisms and a new proposed microsphere-based Luminex assay, may enable molecular identification of *A. fumigatus* without sequencing. However, these methodologies are quite time consuming and labour demanding and are thus impractical in most clinical labs. In addition, they can be very expensive when employed to study collections of large numbers of isolates (Serrano et al., 2011).


Alignment of β-tubulin sequences from species of section *Fumigati*.

As reported by Balajee et al. (2009) the molecular identification scheme was as follows:

Genomic DNA was extracted from aspergilli grown for 48 h on Sabouraud dextrose agar plates by using a DNeasy tissue kit (Qiagen, Valencia, CA). Universal fungal primers directed to the ITS1-5.8S-ITS2 and the β-tubulin regions were employed to amplify DNA from all *Aspergillus* isolates, as described previously. The resultant PCR amplicons were purified by using an ExoSAP-IT enzyme system (USB Corporation, Cleveland, OH), according to the manufacturer's instructions. Sequencing of both strands (with the same primers used for PCR amplification) was performed with a BigDye Terminator (version 1.1) cycle sequencing kit (Applied Biosystems). All cycle sequencing reactions were performed on a GeneAmp PCR system 9700 thermocycler (Applied Biosystems) by using an initial denaturation at 96°C for 5 s, followed by 30 cycles of 96°C for 10 s, 50°C for 5 s, and 60°C for 4 min. The products were purified with an Agencount CleanSEQ system (Beckman Coulter, Beverly, MA), dried, resuspended in 0.1 mM EDTA, and run on a 3730 DNA analyzer (Applied Biosystems) using of the protocols supplied by the manufacturer. The resultant nucleotide sequences were edited by using the Sequencher program (Gene Codes Corporation, Ann Arbor, MI) and aligned by using the program CLUSTAL W. Gene sequences derived from the ITS1-5.8S-ITS2 and the β-tubulin regions of all the *Aspergillus* isolates were compared with sequences in the GenBank database to identify isolates to the species complex level and to the species level within the complex.
Rapid detection of Aspergillus spp. DNA from respiratory and serum samples using Real-Time PCR

Effective extraction of fungal DNA from respiratory samples

Aspergillus niger PCR Detection Kit [32900] : Norgen Biotek
Aspergillus niger PCR Primer Set and Controls

Aspergillus fumigatus PCR Detection Kit
New rtPCR kit to detect Aspergillus infection,
8.4. Serological techniques

8.4.1. Antigen detection in the diagnosis of invasive aspergillosis

In his excellent review on the diagnosis of invasive aspergillosis, Verweij (2005) mentioned that *Aspergillus* species are known to release exo-antigens during growth in vitro and in vivo. Low levels of antigens may be present in body fluids of patients with invasive *Aspergillus* infection such as serum, urine and CSF. A number of methods have been developed and evaluated which employ antibodies directed against antigens produced by Aspergillus. These methods include:

1. latex agglutination: Detection limit 15 ng/ml
2. radioimmunoassay: Detection limit 10 ng/ml
3. ELISA inhibition: Detection limit 5 ng/ml
4. sandwich ELISA: Detection limit 1 ng/ml

8.4.1.1. Detection of *Aspergillus* galactomannan

Two antigen detection kits are commercially available and have been evaluated in several institutes.

The latex agglutination (LA) test (Pastorex Aspergillus, Sanofi Diagnostics Pasteur, Marnes-La-Coquette, France) employs the rat monoclonal antibody EB-A2 to detect *Aspergillus* galactomannan.

Recently, a sandwich enzyme-linked immunosorbert assay (ELISA) was developed (Platelia® *Aspergillus*, Sanofi Diagnostics Pasteur) which employs the same monoclonal antibody as the latex agglutination test. The detection limit of the sandwich ELISA was lowered 10-fold by employing the monoclonal antibody as a captor and detector, thus allowing 0.5 to 1.0 ng/ml of galactomannan to be detected. Several investigations have shown that the sensitivity of the sandwich ELISA was higher that that of the LA-test.
The assay was originally designed for serum, but has also been used on bronchoalveolar lavage fluid (BAL), sputum, CSF, pleural fluid, pericardial fluid and tissue. The generally accepted cutoff in serum for positives is 0.5.

The higher the OD the greater the likelihood of invasive aspergillosis. No cutoff has been defined for any other specimen type, but in BAL fluids different authors have recommended cutoffs from 1.0 to 2.0. This variation partly reflects different patient populations and different dilution factors during bronchoalveolar lavage.

Overall specificity of Aspergillus antigen detection using the galactomannan EIA is approximately 80%. Several antibiotics and other patient factors may yield false positives. Several beta-lactam antibiotics are manufactured using fungal fermentation as a first step. This often results in carryover of galactomannan into the antibiotic preparation and ‘false positive’ galactomannan results that can persist for some days. The most common antibiotics to be implicated are piperacillin/tazobactam (Tazocin) False positive reactivity of the ELISA was found in up to 8% of serum samples and occurred especially with samples obtained within 30 days of BMT or cytotoxic chemotherapy, and in premature infants. False positive reactivity in a single serum sample can be overcome by performing ELISA with additional serum samples and most investigators now define positive as two separate positive samples. If positive, other tests and procedures are required to localise and confirm the presence of infection.

8.4.1.2. Detection of 1,3 β-D-Glucan (BDG)

As mentioned by Barton (2013), the cell walls of Aspergillus contain relatively large amounts of glucan of which 1,3-D-glucan forms a large part. In vitro analysis of growing A. fumigatus showed that, like GM, BDG is released during logarithmic growth, though slightly later.

BDG can be detected through a pathway in the Limulus amoebocyte lysate (LAL) coagulation cascade that has traditionally been used for the detection of bacterial endotoxin. Whilst endotoxin interacts with LAL via factors B and C, factor G in the LAL interacts with BDG activating a proclotting enzyme which can then cleave a chromogenic substrate to generate a product detectable by spectrophotometry down to 10 pg/mL.

There are four different commercial assays for the detection of BDG in clinical specimens. The Associates of Cape Cod Fungitell kit uses amoebocyte lysates from Limulus polyphemus while the Seikagaku Fungitec-G test uses reagents from Tachypleus tridentarius as does the Wako β-Glucan test. Recommended cutoffs for reporting positive results vary between assays. Manufacturers of the Fungitell assay requires >80 pg/mL to be detected for a positive with 60–79 pg/mL Cutoffs for the T. tridentatus based assays are lower at 20 pg/mL and even lower
cutoffs of 11 pg/mL or two sera at 7 pg/mL have been proposed. A fourth assay, GKT-25-M has been reported in the Chinese literature.

8.4.2. *Aspergillus* antibody detection

There are multiple marketed IgG antibody tests to detect *A. fumigatus* antibodies. A smaller number of less well used and often usually incompletely validated tests are available for other species of *Aspergillus* including *A. flavus, A. terreus, A. niger, A. versicolor* and *A. clavatus*. All testing is on serum. There are multiple marketed IgG antibody tests to detect *A. fumigatus* antibodies, including Immy, Serion/Virion, Bioenche, BioRad, Thermofisher, Elitech, and Microgen.

8.4.2.1. *Aspergillus* Immunodiffusion test

- The ID test is very helpful in the diagnosis of ABPA and aspergilloma, the two forms of aspergillosis observed in immunocompetent individuals where infection can be correlated with a rise in specific antibodies. Precipitins can be found in >90% of patients with aspergilloma and in 70% of patients with ABPA.
- In contrast to immunocompetent hosts, growth of *Aspergillus* in the tissues of an immunosuppressed host does not correlate with an increase in anti-*Aspergillus* antibody titers. The parallel use of ID and CF tests and clinical data is an effective means for specific diagnosis of Aspergillosis. Precipitins can be found in >90% of patients with aspergillomas and in 70% of patients with ABPA.
- The greatest number of Aspergillosis cases may be detected by the use of *A. fumigatus, A. flavus, A. niger,* and *A. terreus* antigens in separate ID tests performed at the same time. Precipitins are less frequent in patients with invasive Aspergillosis.
In fact, the presence of anti-Aspergillus antibody in immunocompromised individuals is more likely to represent antibody formed before the onset of immunosuppressive therapy rather than as a result of invasive infection.

An increase in antibody titer at the end of immunosuppression is indicative of recovery from IA, whereas absence of an antibody titer or declining antibody levels suggest a poor prognosis. Thus, antibody detection can be used prognostically but not diagnostically for IA.

Two or more distinct precipitin lines should be formed when A. fumigatus reference antiserum is allowed to react with A. fumigatus antigen. One or more distinct precipitin lines should be formed when A. flavus, A. niger, or A. terreus reference antiserum is allowed to react with the homologous antigen.

Because the Aspergillus antigens of diagnostic significance have not been defined, any precipitin band (whether identity, partial identity, or non-identity) is significant and the number of bands should be reported.

The demonstration of one or more precipitins indicates infection, including aspergilloma. Precipitating antibodies are often detectable in serum from patients with ABPA. Although one or two precipitins can occur with any clinical form of Aspergillosis, the presence of three or more bands is invariably associated with either an aspergilloma or IA. The test may be negative for some patients receiving long-term antifungal or corticosteroid therapy. When used with reference antisera the ID test is 100% specific.
8.4.2.2. Aspergillus Antibody, Complement Fixation test

Single titers $\geq 1:32$ are indicative of recent infection. Titers of $1:8$ or $1:16$ may be indicative of either past or recent infection, since CF antibody levels persist for only a few months. A four-fold or greater increase in titer between acute and convalescent specimens confirms the diagnosis. Sensitivity of the CF test for aspergillosis is lower than that of the immunodiffusion test. Crossreactions may occur in patients with histoplasmosis and coccidioidomycosis. This test is approved for New York patient testing.

Comments of Richard C. Barton (2013) on methods of laboratory diagnosis of aspergillosis

- Of the wide variety of methods reviewed of diagnosing invasive aspergillosis, direct microscopy and histopathology are undoubtedly the most subjective, skilled, and labour intensive.
- Though histopathological detection of Aspergillus of tissue will remain an essential capacity and help define the highest level of certainty in diagnostic criteria, less invasive and more rapid methods have already overtaken this approach in most settings. Some will also consider that traditional culture-based methods may also be superceded by DNA and antigen detection methods.
- However, in the recent US PATH registry update culture of Aspergillus for the diagnosis of IA was still the most frequent laboratory approach. Furthermore, cultures of Aspergillus allow further analysis such as susceptibility to testing, recent developments in direct molecular detection of resistance notwithstanding, and the possibility of molecular typing in epidemiological investigations. Furthermore, new species of Aspergillus causing invasive disease continue to be uncovered by culture whose applicability to serological and molecular detection cannot be assumed. Culture of respiratory specimens in clinical laboratories is unlikely to be abandoned in the near future and culture of Aspergillus will remain an important if generally insensitive approach to the diagnosis of IA.
- The detection of galactomannan in clinical specimens is firmly established as the test of choice for any laboratory providing diagnostic services for patients at risk of IA. Serum detection remains a key approach and amenable to serial measurements whilst BAL material appears to have a higher sensitivity but is often harder to obtain. False positives are less of an issue than is often claimed with antibiotic sources of GM now rarely seen and neonatal samples likely to account for a tiny fraction of samples analysed. Sensitivity is clearly affected by antifungal treatment, though the biological basis for this is unclear, this remains the main limitation to the use of the assay particularly in patients undergoing antifungal prophylaxis. A plethora of meta-analyses have confirmed the clinical value of GM testing and at least some analyses of GM serum kinetics point to the potential for this
assay to guide therapy beyond diagnosis. The BDG assay has yet to be widely adopted as a diagnostic tool, perhaps suffering from the need to also require more specific diagnostic methods to target therapy in positive patients. Meta-analysis suggests that problems with specificity were probably overestimated in initial studies and sensitivity is comparable with GM. The BDG assay will probably find its place in some centres in carefully designed care pathways where the negative predictive value can be used to reduce empiric therapy. The PCR assay to detect Aspergillus DNA held a large amount of promise but has been limited up until recently by a lack of standardisation. The scientists of EAPCRI have nobly met the challenge of technical diversity in PCR assays and provided meticulously researched standard methods for extraction of DNA from whole blood and serum.

9. Treatment of aspergillosis

As mentioned by Mayo Clinic Staff, the following guidelines are recommended:

1. **Observation.** Aspergillomas often don't need treatment, and medications aren't usually effective in treating these fungal masses. Instead, aspergillomas that don't cause symptoms may simply be closely monitored by chest X-ray.

2. **Oral corticosteroids.** The goal in treating allergic bronchopulmonary aspergillosis is to prevent existing asthma or cystic fibrosis from becoming worse. The best way to do this is with oral corticosteroids. Antifungal medications by themselves aren't helpful for allergic bronchopulmonary aspergillosis, but they may be used in combination with corticosteroids to reduce the dose of steroids and improve lung function.

3. **Antifungal medications.** These drugs are the standard treatment for invasive pulmonary aspergillosis. Historically, the drug of choice has been amphotericin B, but the newer medication voriconazole (Vfend) is now preferred because it appears more effective and may have fewer side effects. All antifungals can cause serious problems, however, including kidney and liver damage, and they frequently interact with other medications given to people who have weakened immune systems.

4. **Surgery.** Because antifungal medications don't penetrate aspergillomas very well, surgery to remove the fungal mass is the first-choice treatment when bleeding from the mass in the lungs occurs. But the surgery is risky, and your doctor may instead suggest embolization. In this procedure, your doctor, usually a radiologist, threads a small catheter into the artery that supplies blood to the cavity containing the fungus ball, and injects a special material that clogs the artery. Though this procedure can stop massive bleeding, it doesn't prevent it from recurring, so it's generally considered a temporary treatment.
Therapeutically Important Antifungal Agents (Khan, 2013)

1. Polyene Antibiotic (Amphotericin B):

- Amphotericin B (AmB) is a polyene (containing multiple double bonds) macrolide antibiotic originally isolated from a *Streptomyces* species. It binds to ergosterol, a component of the fungal cell membrane. Binding to ergosterol destroys fungal membrane integrity, resulting in leakage of cellular content and then cell death. Being highly insoluble in water and in its original formulation, AmB was complexed with deoxycholate.

- AmB is poorly absorbed orally and requires parenteral administration. Following IV administration, the drug is released slowly and is highly bound to protein (>90%). AmB accumulates significantly in the liver and spleen, and it is present in synovial, pleural, and peritoneal fluid. Central nervous system (CNS) penetration is minimal. AmB has a half-life of 15 days and is excreted very slowly from the kidney.

- AmB adverse effects (AEs):
  1. **Infusion reactions** include fever, shaking, chills, hypotension, and tachypnea.
  2. **Renal toxicity** is characterized by renal ischemia, hypokalemia, and tubular acidosis.
  3. **Reduction of the production of erythropoietin** (a glycoprotein that stimulates bone marrow to produce RBCs) in the kidney.

- AmB should not be administered concurrently with other nephrotoxic agents (aminoglycosides, nonsteroidal anti-inflammatory drugs).

- Serious AEs have prompted the development of lipid formulations of AmB. Lipid formulations that minimize the renal toxicity of AmB are AmB colloidal dispersion (ABCD), liposomal AmB (L-AmB), and AmB lipid complex (ABLC). These formulations have largely replaced AmB.

2. Azoles (Voriconazole, Posaconazole, Itraconazole):

Chemically, azoles are triazole derivatives. These agents act by inhibiting fungal sterol-14-alpha-demethylase, a cytochrome-dependent enzyme associated with ergosterol synthesis. Inhibition of this enzyme enables the accumulation of methylsterol, thus impairing other cellular functions. The main azoles are:

1. **Voriconazole** is formulated for oral and parenteral administration. Minimally bound to plasma proteins, it is metabolized in the liver by CYP enzymes (CYP3A4, CYP2C9, CYP2C19) and also inhibits these enzymes. Voriconazole is excreted renally. Transient
visual disturbances (blurred vision, changes in color vision or brightness) are associated with this drug.

2. **Posaconazole** is administered orally as a suspension. Its absorption is increased with food. Posaconazole is metabolized by glucuronidation and is excreted in the feces. The drug inhibits CYP3A4 and is a substrate of P-glycoprotein (PgP). AEs include headache and GI distress.

3. **Itraconazole**
   i. **Itraconazole** is available in oral and parenteral formulations. It is absorbed well orally in the presence of food and low pH and is excreted fecally.
   ii. Itraconazole is significantly bound to plasma proteins and is metabolized by CYP3A4. Hydroxyitraconazole is an active metabolite of the parent drug.
   iii. Itraconazole inhibits CYP enzymes and PgP, and it results in liver toxicity.
   iv. Itraconazole has a negative inotropic effect on the heart and should not be used in patients with ventricular dysfunction or congestive heart failure.

4. **Echinocandins (Caspofungin, Micafungin):** 
   These agents inhibit 1,3-beta-glucan synthase, an enzyme responsible for fungal cell wall synthesis.
   i. Echinocandins have selective toxicity against fungi because mammalian cells do not possess a cell wall.
   ii. Echinocandins are semisynthetic lipopeptides and are administered IV only. These agents are significantly bound to plasma proteins (>95%), and CNS penetration is inadequate.
   iii. Echinocandins are excreted predominantly via the feces. Echinocandins do not induce or inhibit CYP enzymes, nor do they interact with PgP. As a result, the potential for drug interactions with other therapeutic agents is negligible.
   iv. Echinocandins are usually well tolerated, and the most common AEs are elevated liver enzymes and creatinine (Cr), histamine-mediated effects (rash, pruritus, facial swelling), GI distress, headache, and pyrexia.
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166


