THE NORTHERN HOSPITAL

AMPHOTERICIN B

Detail of a miniature of Pope Joan giving birth, from Giovanni Boccaccio's De Claris Mulieribus, France (Rouen), c. 1440, Royal MS 16 G V, f. 120r.

After Leo, an Englishman born at a Mainz, was Pope for two years, seven months and four days, and died in Rome, after which there was a vacancy in the Papacy for one month. It is claimed that this John was a woman, who as a girl had been brought to Athens in the clothes of a man by a certain lover of hers. There she became proficient in a diversity of branches of knowledge until she had no equal.; and afterwards in Rome, she taught the liberal arts and had great masters amoung her students and audience. In the city the opinion of her life and learning grew ever higher, and she was the unanimous choice for Pope. While, Pope, however, she became pregnant by her companion. Through ignorance of the exact time when the birth was expected, she was delivered of a child while in procession from St. Peter's to the Lateran, in a narrow lane between the Coliseum and St. Clements's Church. After her death, it is said that she was buried in that same place. The Lord Pope always turns aside from this street and it is believed by many that this is done because of abhorrence of the event. Nor is she placed on the list of the holy pontiffs both because of her female sex and on account of the shamefulness of the event.

Martin of Troppau, Chronicon Pontificum et Imperatum, 1265 A.D

Thanks to the immense popularity of Martin of Troppau's Chronicle the legend of a Ninth century female Pope, by the name of Joan, but who supposedly took the name of John VII (or VIII), became, as John Julius Norwich has described it, one of the "hoariest canards" in the history of the Papacy! Though most modern day historians dismiss the story of the female Pope as myth, she still has some adherents! Pope Joan was said to have reigned between Pope Leo IV and Benedict III, from 855 - 857 A.D. This period of the "Dark Ages" is very poorly documented, and we know virtually nothing of many of the Popes during the Ninth century, which only adds to the confusion. Legend has it that Pope Joan (or "John") was only discovered to be a woman, when by a misfortune of exquisitely poor timing, she gave birth in a narrow street whilst on holy procession from St. Peter's to the Lateran. The people, to say the least, were shocked speechless, and the inevitable lynching supposedly followed. Another Thirteenth century Dominican Friar by the name of Jean de Mailly, in his Chronica Universalis Metensis recorded his version of the story, as well as Joan's end…

…concerning a certain Pope or rather female pope, who is not set down in the list of popes or bishops of Rome, because she was a woman who disguised herself as a man and became by her character and talents, a curial secretary, then a cardinal and finally a pope, one day while mounting her horse, she gave birth to a child. Immediately, by Roman justice, she was bound by the feet to a horse's tail and dragged and stoned by the people for half a league. And where she died there she was buried and at the place is written Petre Pater Patrum Papisse Prodito Partum (Oh Peter, Father of Fathers, betray the Childbirth of the Woman Pope). At the same time the four day fast called "the fast of the female pope", was first established.

In the Thirteenth century the story of Pope Joan was widely believed in the popular mind, and indeed in the minds of many within the Vatican itself. Bartolommeo Platina the distinguished Prefect of the Vatican Library under Sixtus IV (1471-1484) inserted "John VIII" between Leo IV and Benedict III, in his "Lives of the Popes", but added, "These things which I relate, are popular reports, but are derived from uncertain and obscure

authors, which I have therefore inserted briefly and baldly, lest I should seem obstinate and pertinacious by omitting what most people assert…although what I have related may not be thought altogether incredible"

The Welshman, Adam of Usk, who was in Rome (1402 - 1406), during the coronation of Innocent VII, left an intriguing account of a statue of Pope Joan. During the procession of Innocent VII from St. Peter's to the Lateran, he states, "After turning aside out of abhorrence for Pope Agnes (sic - i.e Joan), whose image in stone with her son stands in the straight road near St. Clements's, the Pope, dismounting from his horse, enters the Lateran for his enthronement". This statue, supposedly marking the place where Pope Joan gave birth, appears to have existed for around a century, possibly longer, before Sixtus IV around 1480, had it thrown into the Tiber. But successive Popes apparently continued to deliberately avoid the site. Johannes Burckhardt, Bishop of Strasbourg and Papal Master of Ceremonies under Innocent VII (1484 - 92) ruefully recorded how Innocent was brave enough to break with tradition:

"…In going, as returning, Pope Innocent came by way of the Colosseum, and that straight road where the image of the female Pope is - in token - it is said that John VIII (sic) gave birth there to a child. For that reason, many say the Popes may never ride on horseback there. And so the Lord Archbishop of Florence…reprimanded me".

Indeed for many years another statue dedicated to Pope Joan existed in the Cathedral of Sienna. In the Thirteenth century it was placed among the busts of 170 other Popes all in chronological order up to the time of Pope Lucius III who died in 1185. She was placed, sure enough, between Leo IV and Benedict III and dutifully labeled "Johannes VIII, Foemina de Anglia". Sadly Clement VIII had it removed in 1600, although Antoine Pagi, early in the Seventeenth century, recorded that Pope Joan's bust rather than being destroyed underwent some minor remodeling and was then relabeled as Pope Zachary (741-52)!

But for perhaps the most astonishing "artifact" relating to the story of the female Pope, we return to Adam of Usk again who describes a certain chaise percee type of artifact:

"…And there in the Lateran he is seated in a chair of porphyry, which is pierced beneath for this purpose, that one of the younger cardinals may make proof of his sex; and then, while a Te Deum is chanted, he is borne to the high altar.

John Julius Norwich narrates a second fuller description, of this startling practice of ensuring against any future embarrassments by a certain Felix Haemerlein in his De Nobilitate et Rusticitate Dialogus of circa 1490:

"…up to the present day the seat is still in the same place and is used at the election of the pope. And in order to demonstrate his worthiness, his testicles are felt by the junior cleric as testimony of his male sex. When this is found to be so, the person who feels them shouts out in a loud voice "He has testicles!" and all the clerics present reply "God be praised!" then they proceed joyfully to the consecration of the pope-elect".

Haemerlein goes on to explain that this important procedure in the election of Popes was to ensure against any future surprises and that the perforated chair was set up by Pope Joan's successor, Benedict III, (but failed to mention whether or not Benedict himself underwent testing by the chair). It seems that two such chairs were constructed. One apparently remains today in the Vatican Museum and apparently does indeed have a large keyhole cut into the seat! The other was looted by Napoleon's army in the early Nineteenth century and supposedly taken away to the Louvre, but Norwich narrates that modern day Louvre officials deny this. Our most reliable historical sources state that Leo IV died on 17 July 855 and that Benedict III was consecrated on 29 September 855. So unless Pope Joan reigned for just two months, (..though plenty of Popes have reigned for less…John Paul I for one…), then there is simply no time for a two year reign of Pope Joan. Today most historians discount the story of Pope Joan…but…one can't help wondering about that peculiar chair in the Vatican Museum!

When we prescribe the antifungal agent amphotericin B, we need recall the unfortunate legend of Pope Joan! The dosages and infusion rates for this drug are complex and expert guidance will be required. Indeed there are no less than three different formulations (conventional, lipid complex and liposomal) and these are significantly different agents, all with different dosing regimes. Just as Pope Joan showed exceptionally poor planning with respect to the timing of her delivery, with fatal results, so poor planning in dosing with amphotericin may similarly lead to fatal results!

Johanna Wokalek as Pope Joan, in "Die Papstin", Constantin Film, 2009

AMPHOTERICIN B

Introduction

Amphotericin B is a polyene antifungal produced by the growth of certain strains of *Streptomyces nodosus.*

Oral amphotericin B is not absorbed to a significant degree and is used to treat oral fungal infections.

IV Amphotericin B is used for the treatment of a wide range of serious systemic or deep fungal infections.

Conventional **IV** Amphotericin B **deoxycholate** has significant toxicity.

Liposomal and **lipid complex amphotericin B** are newer less toxic formulations for intravenous use.

History

Amphotericin was originally extracted from *Streptomyces nodosus*, a filamentous bacterium, in 1955.

It was extracted from cultures of an undescribed streptomycete which was isolated from soil collected in the region of the **Orinoco River** in **Venezuela.**

Chemistry

Amphotericin is a mixture of antifungal polyenes produced by the growth of certain strains of Streptomyces nodosus. It consists largely of **amphotericin B**.

Amphotericin A is much less potent in vivo, and not used clinically.

Classification

The five classes of antifungal agents are:

1. Polyenes:

   These include:

   - **Amphotericin B**
   - Nystatin

2. Azoles:

Azole antifungal drugs (except for abafungin) inhibit the fungal cytochrome P450 enzyme lanosterol 14 α-demethylase. This enzyme is necessary to convert lanosterol to ergosterol. Depletion of ergosterol in fungal membrane disrupts the structure and many functions of fungal membrane leading to inhibition of fungal growth

- Imidazoles

  These include:

  - ♥ Clotrimazole
  - ♥ Econazole
  - ♥ Ketoconazole
  - ♥ Miconazole

- Triazoles:

  Systemic agents include:

  First generation agents:

  - ♥ Fluconazole
  - ♥ Itraconazole

  Second generation (extended spectrum) agents:

  - ♥ Voriconazole
  - ♥ Posaconazole

- Thiazoles

  - ♥ Abafungin

3. Allylamines:

These include:

- Amorolfin
- Butenafine
- Naftifine

- Terbinafine

4. Echinocandins:

These include:

- Anidulafungin
- Caspofungin
- Micafungin

5. Others:

These include:

- Griseofulvin
- Flucytosine
- Pentamidine (effective against Pneumocystis jirovecii (previously P. carinii)

Preparation

Lozenge:

- 10 mg

Ampoules:

- **Amphotericin B deoxycholate** (conventional or standard IV preparation)
  - ♥ Amphotericin deoxycholate is not marketed in Australia but may be made available through the SAS (Special Access Scheme).
- **Abelcet** is **lipid complex Amphotericin B** - a less toxic product for intravenous infusion.
- **AmBisome** is **liposomal Amphotericin B** - a lyophilised less toxic product for intravenous infusion.
  - ♥ Each vial contains **50 mg** of amphotericin B, intercalated into a liposomal membrane as a powder for reconstitution with sterile water for injection.

  Liposomes are closed, spherical vesicles formed when certain polar lipids, e.g. phospholipids and cholesterol, are dispersed in water

AmBisome contains single bilayer liposomes with the drug held in the membrane as a charge complex with di-stearoyl-phosphatidyl-glycerol. The liposomes are less than 100 nanometers in diameter.

Mechanism of Action

Amphotericin B irreversibly binds to ergosterol in fungal cell membranes causing cell death by altering their permeability and allowing leakage of intracellular components.

It, is fungistatic or fungicidal, depending on the drug concentration attained in body fluids and the susceptibility of the fungus

Mammalian cell membranes also contain sterols such as cholesterol, to which amphotericin B has less binding affinity than to ergosterol. It has been suggested that damage to human cells and fungal cells caused by amphotericin B may share common mechanisms.

Pharmacodynamics

Amphotericin B is an antifungal agent.

It is active against a wide range of yeasts, including *Candida* and *Cryptococcus* species, and other fungi, including most *Aspergillus* species (but not *A. terreus* or *A. nidulans*) some *Fusarium* species, zygomycetes and phaeohyphomycetes, and *Leishmania* species.

It is effective against many fungi, including, *Aspergillus, Candida, or Cryptococcus.*

It is inactive against bacteria (including Rickettsia) and viruses

Reports of amphotericin B resistant fungi are uncommon.

Pharmacokinetics

Absorption:

- There is **little or no** absorption of amphotericin B from the gastrointestinal tract.

  Orally administered amphotericin B cannot be used for the treatment of *systemic* fungal infections.

- Amphotericin B is given by IV infusion for systemic or deep seated fungal infections.

Distribution:

- AmBisome can remain intact in the circulation for prolonged periods and distributes as intact liposomes to tissues where fungal infections may occur.

Both AmBisome and liposomes with the same lipid composition preferentially associate with the outer surface of fungal cell walls.

AmBisome acts by liposome binding to the outer wall of fungi, followed by drug release.

On release, the drug is thought to transfer to the ergosterol rich fungal cell membrane for which it has high affinity.

Interaction with fungi occurs both within and outside macrophages and is believed to be enzymatically mediated.

- The Vd of **AmBisome** is approximately 25 liters.
- Amphotericin binding to plasma proteins > 90 %
- Amphotericin can cross the human placenta
- Amphotericin is considered unlikely to be excreted into human breast milk

Metabolism and excretion:

- The distribution half-life of **AmBisome** ranges from 40- 50 minutes (depending on the dose given.
- The elimination half-life of **AmBisome** is long and ranges from 26 - 32 hours (depending on the dose given).

Indications

These include: [2]

1. Severe *systemic* fungal infections:
    - e.g. fungaemia, deep infections.
2. Empirical treatment in high-risk febrile neutropenic patients unresponsive to antibacterials
3. Cryptococcal meningitis (drug of choice)
4. Treatment and suppression of oral and perioral candidiasis
5. Prevention of systemic candidiasis, aspergillosis and cryptococcosis after liver transplant
6. Secondary prevention or suppression of fungal infection in HIV

7. Visceral leishmaniasis, (seek specialist advice).

8. Amoebic meningitis, (seek specialist advice).

Note that, as for all antibiotics, the prevalence of microbial resistance may vary geographically and over time for selected species and local information on resistance is also important, particularly when treating severe infections.

Contra-indications/precautions

These include:

1. Known hypersensitivity to amphotericin B

    - Or any of the components of the various formulations.

2. Drug interactions:

    - Concomitant treatment with nephrotoxic drugs (e.g. aminoglycosides, cyclosporin) may increase likelihood of renal impairment; avoid combination or monitor renal function closely.

3. Renal impairment/ failure

Pregnancy

Amphotericin B is a category B3 drug with respect to pregnancy.

Category B3 drugs are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Maternal use of amphotericin has not been associated with an increased risk of congenital malformations.

Parenteral amphotericin is considered safe to use for the treatment of life-threatening systemic fungal infections during pregnancy.

However, consultation with an Infectious Diseases specialist or Clinical Microbiologist for further advice is recommended.

Oral amphotericin is safe to use during pregnancy as there is little or no absorption from the gastrointestinal tract.

Breast feeding:

Infants exposed to amphotericin via breast milk are unlikely to experience adverse effects due to the high molecular weight, high protein binding and low oral bioavailability of the medicine.

Amphotericin is considered safe to use during breastfeeding.

Adverse Effects

No systemic adverse effects have followed **oral** administration of up to 3 grams daily

IV amphotericin B (particularly the conventional desoxycholate formulation) can be associated with significant toxic effects.

These include:

1. Allergic reactions:
    - Including anaphylaxis
2. Dermatological hypersensitivity reactions:
    - These can be severe, and include Stevens-Johnson Syndrome/ TEN
3. Infusion reactions:

    These reactions are more likely to occur if the infusion rate is too rapid

    Features include non-specific constitutional symptoms such as:

    - Fever
    - Headache
    - Chills/ malaise
    - Hypotension/ anaphylactoid reactions
    - GIT upset
        - ♥ Anorexia, nausea, vomiting
    - Myalgias/ arthralgias.

    Symptoms usually lessen with continued treatment.

When given over 2 hours, there is a higher rate of **infusion reactions** with amphotericin lipid complex (Abelcet) than with liposomal amphotericin (AmBisome).

Liposomal amphotericin, however may also cause:

- Chest pain
- Hypoxia/ dyspnoea
- Severe abdominal/ flank/ leg pain
- Flushing / urticaria

These reactions may be related to the liposomal component; but frequency is very variable.

4. Nephrotoxicity:
    - Increased serum creatinine
    - Hypokalemia
    - Hypomagnesaemia
    - Hyponatremia
    - Oliguria or anuria
5. Hyperkalaemia in renal impairment

More minor reactions may include:

6. Anaemia
7. Thrombophlebitis
8. Hyperglycaemia
9. Elevated liver enzymes.

Dosing

Exact dosing and duration of dosing depends on the condition being treated as well as it severity.

In general terms:

Oral lozenge:

One lozenge should be sucked and allowed to dissolve slowly in the mouth **4 times a day** for a duration of 7 - 14 days.

The lozenges should be taken after meals and at bedtime. Patients wearing dentures should be especially careful to cleanse them thoroughly and to remove them while sucking the lozenge to allow the active material to reach all tissues.

IV:

Note that the dosage and infusion rates for each amphotericin formulation (conventional, lipid complex or liposomal) are significantly different - exercise caution when prescribing and administering, because errors have caused fatalities. [1]

Patients should be prehydrated with sodium chloride 0.9% (0.5 to 1 liter IV) before the commencement of amphotericin infusion.

For Liposomal (AmBisome) [2]

- **Adult, child, IV, start at 1-3 mg/kg once daily,**

  Increase gradually up to 5 mg/kg once daily if necessary for severe infection.

  Lower doses may be effective but clinical trial data are limited.

  Higher doses have been used but may be more nephrotoxic.

  Cumulative dose of 60 grams over 9 months has been given without significant toxicity.

  For Liposomal amphotericin (AmBisome) infusion rates IV should be over 30 - 60 minutes at a concentration of 0.2–2 mg/mL in 5% glucose.

Treatment of Infusion Reactions:

Infusion reactions are generally treated along similar lines to anaphylactoid reactions:

Therefore:

- Temporarily cease the infusion, and restart at a slower rate when symptoms are stabilized.
- Fluids as required
- Antihistamines
- IV paracetamol

Johanna Wokalek as Pope Joan, in "Die Papstin", Constantin Film, 2009

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