

# Selection of an optimal antifungal for treatment of invasive aspergillosis:

susceptibility/resistance, adverse reactions,  
drug interactions

John Bennett, M.D.

# Disclosures

- No disclosures to report



# Choices for aspergillosis

Polyene: liposomal (AmBisome), lipid complex (ABLIC)

Intravenous or oral azole: Voriconazole, Isavuconazole

Intravenous echinocandin: caspofungin, micafungin?

Oral only azole: posaconazole, itraconazole

# Issues in drug choice

- Can the patient take oral alimentation?
- How urgent is the need for Rx?
- Is the Aspergillus species known?
- Are drug interactions manageable?
- How tenuous is the patient's renal function?
- How certain do we need to be that the drug is effective?

# Oral alimentation

- Posaconazole levels up 2.6 fold with nonfat food; 4 fold up with fatty meal
- Response improved with higher level
- | Quartile of blood level | C <sub>av</sub> (ng/ml) | Improved with posa |
|-------------------------|-------------------------|--------------------|
| 1                       | 124                     | 24% (4/17)         |
| 2                       | 411                     | 53% (9/17)         |
| 3                       | 719                     | 53% (9/17)         |
| 4                       | 1250                    | 75% (12/16)        |
- Walsh, CID 2007:44:2-12

# Urgency: time to steady state

- Posaconazole: 5-7 days to steady state. Loading not possible.
- Itraconazole: IV no longer available. Oral loading over 3 days.
- Voriconazole, echinocandins, amphotericin B: loading in 24 hrs or less

# Ampho B resistance in *Aspergillus terreus*

- 3-5% isolates are *A. terreus*
- Walsh JID 2003: Exp infection response to ampho poor
- Steinbach, AAC 2004: Am B MIC 4X higher
- Hachem, Cancer 2004: 28% response to ampho with *A. terreus*, 39% with *A. fumigatus*
- Lass-Flörl, Brit J Hem 2005: compared 32 pts with *A. terreus* vs 35 with other Asp species: Infection more often disseminated (63% vs 32%) and poorer response to ampho 21% vs 46%

# DRUG-DRUG INTERACTIONS

- Voriconazole has many interactions, posaconazole slightly less
  - Blood levels of many drugs increased
  - Azole levels down with rifampin, rifabutin, efavirenz, Tegretol, phenytoin, other
- Echinocandin interactions with other drugs not significant though caspo levels down 30% with rifampin

# Renal function and antifungals

- Liposomal ampho less nephrotoxic than ABLC; both less toxic than conv. Am B. Saline loading decreases nephrotoxicity
- IV voric exipient (sulfobutyl cyclodextrin) accumulates, may not be toxic.
- No adjustment for oral voric, caspofungin, micafungin

# Efficacy in Rx of Aspergillosis

- Initial Rx: voriconazole, ampho formulations approved
- Salvage Rx
  - Caspofungin
  - Posaconazole (Europe)

# Micafungin or Caspofungin in Salvage Therapy of Invasive Aspergillosis

Complete or Partial Response to  $\geq 1$  dose

Micafungin Caspofungin

Primary Therapy

6/12 (50%)

N/A

Salvage Therapy

Intolerant

3/4 (75%)

9/12 (75%)

Failure


6/18 (33%)

28/59 (47%)

Issues: Micafungin dose 75-225 mg. What is intolerant?  
How long was the failing drug given?

Denning et al. *J Infect.* 2006; Maertens et al. *Clin Infect Dis.* 2004; 39: 1563-71.

# What about combination therapy?

- Synergy *in vitro* unimpressive
  - Experimental animal infections show slight advantage with combination over individual drugs if doses are low
  - Clinical data on combinations are not convincing
- 

## COMBINATION THERAPY

### Chart reviews of voriconazole +caspofungin for invasive aspergillosis at the Fred Hutchinson Cancer Research Center

- Salvage Rx: V+C in 16 pts had better 3 mos survival than earlier (1997-2001) group of 31 pts with V alone. Marr CID 2004; 39:797
- Initial Rx: 90 day survival in I.A. improved from ca. 28% to ca 45% between 1996-2004. No survival advantage for V+C as initial Rx. Upton CID 2007;44:531

# AmBisome +/- Caspofungin in IA

## Randomized open trial 9 French centers (Caillot Cancer 2007;110:2740)

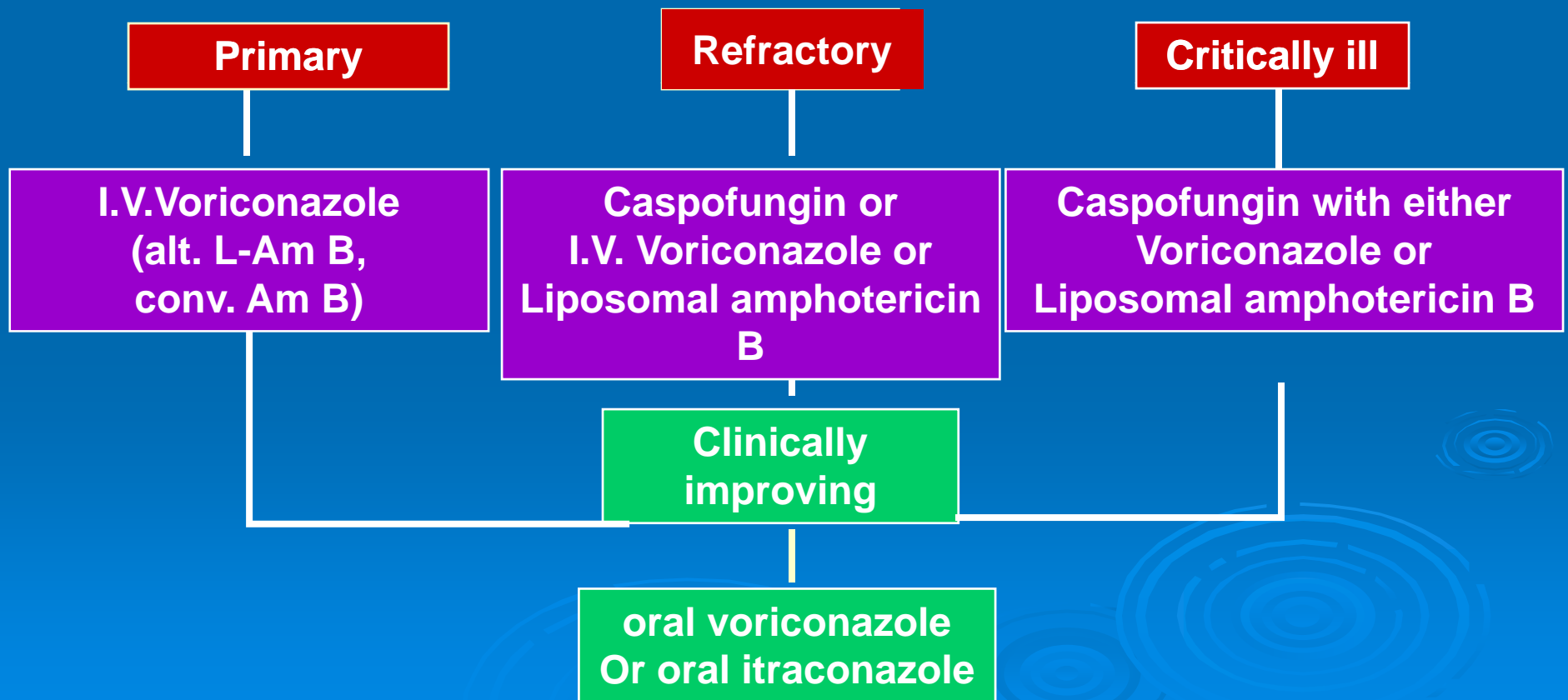
	AmBiLoad trial*			
	AmB 3 mpk +C	AmB 10 mpk	3mpk	10 mpk
# pts	15	15	107	94
Median days to EOT	18	17	15	14
Response at EOT				
Improved	10 (67%)	4 (29%)	50%	46%
Stable	4	6		
Failed	1	4		
Unknown	0	1		
Survived 12 wks	15/15	12/14 (86%)	72%	59%

\*Cornely CID 2007

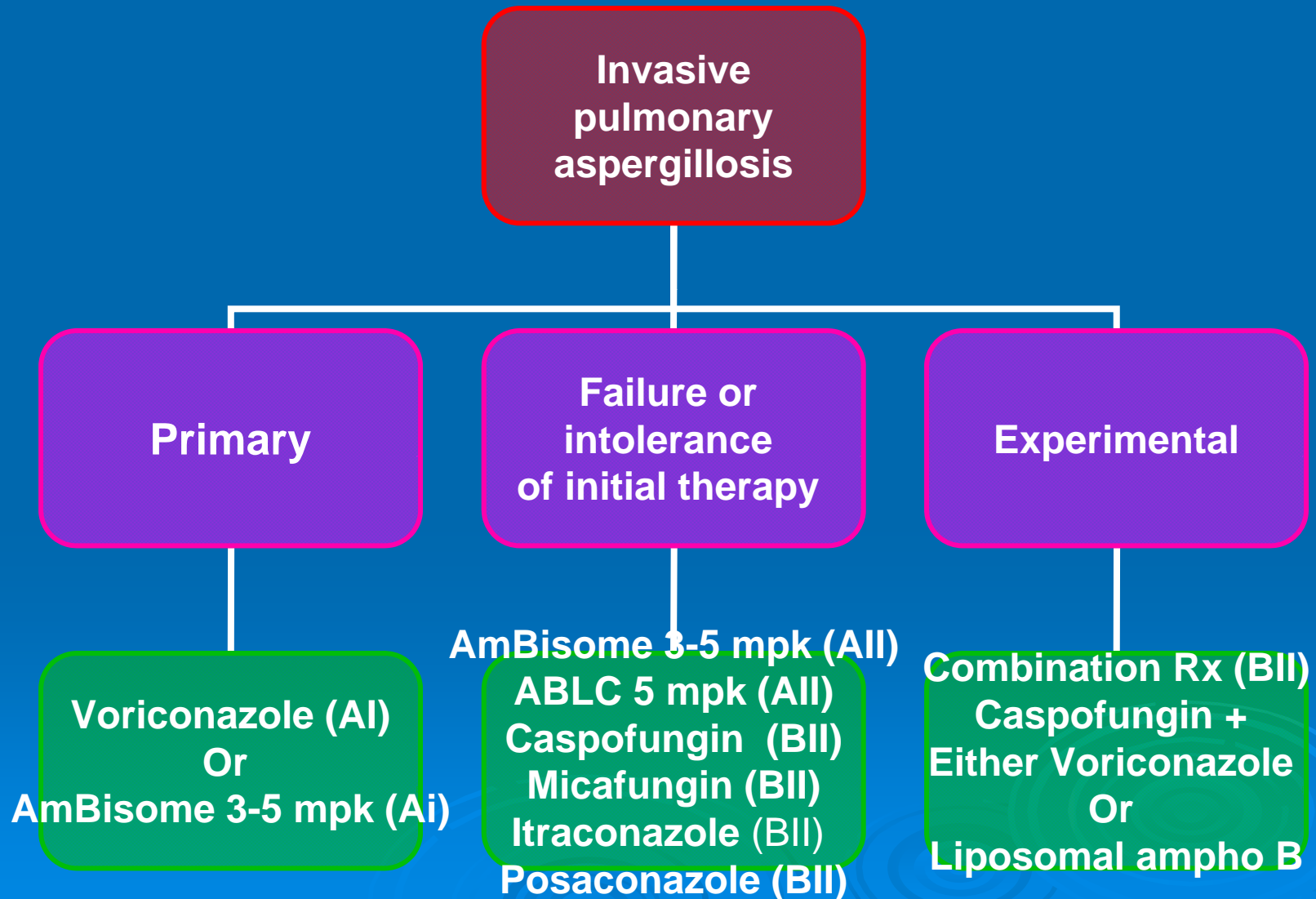
# Therapy of Invasive aspergillosis

## Recommendations of the Fungal Infection Network of Switzerland

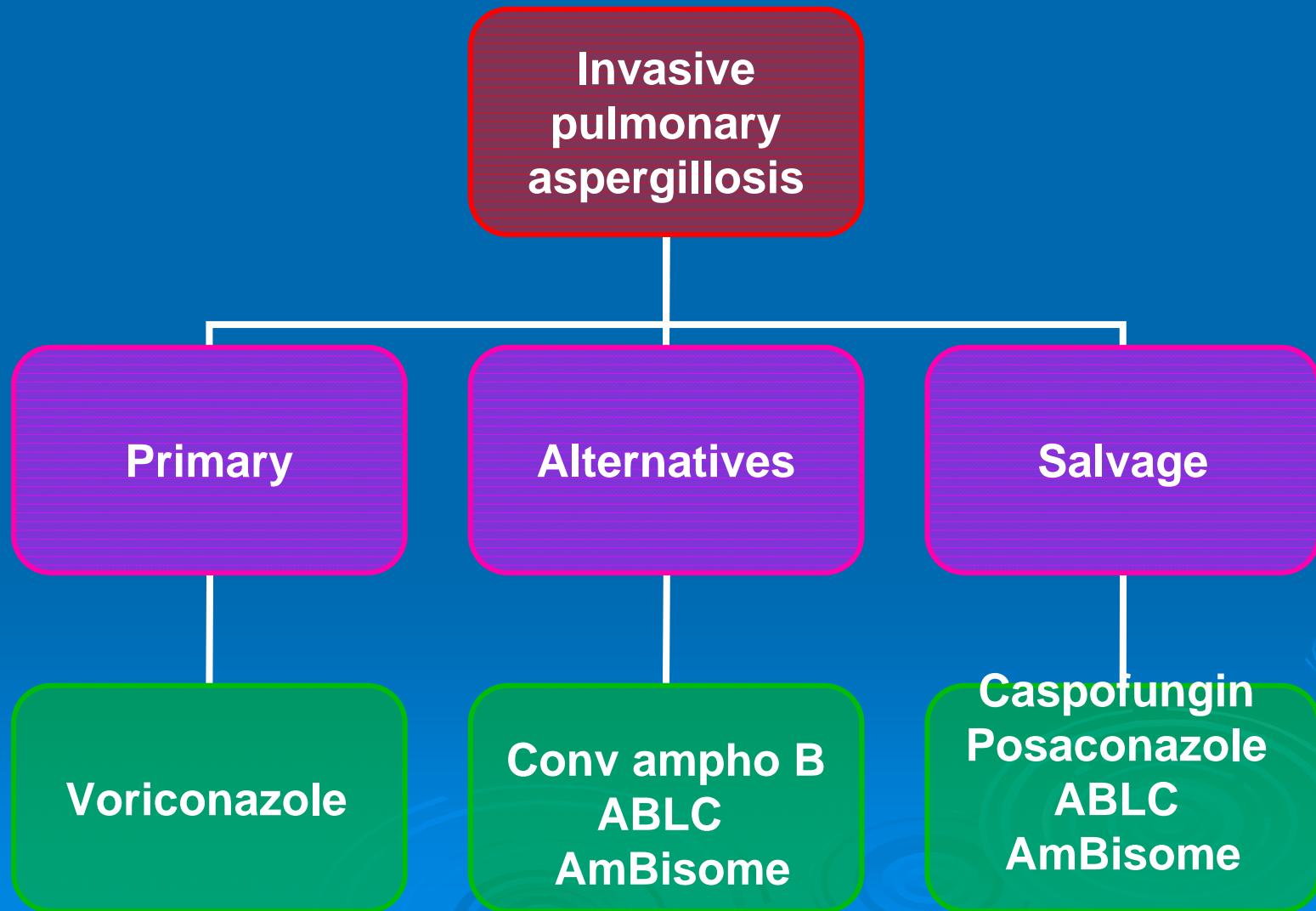
(Swiss Med Wkly 2006; 136:447-463)



# Summary of Recommendations of the IDSA for Treatment of Aspergillosis (CID Feb 2008)

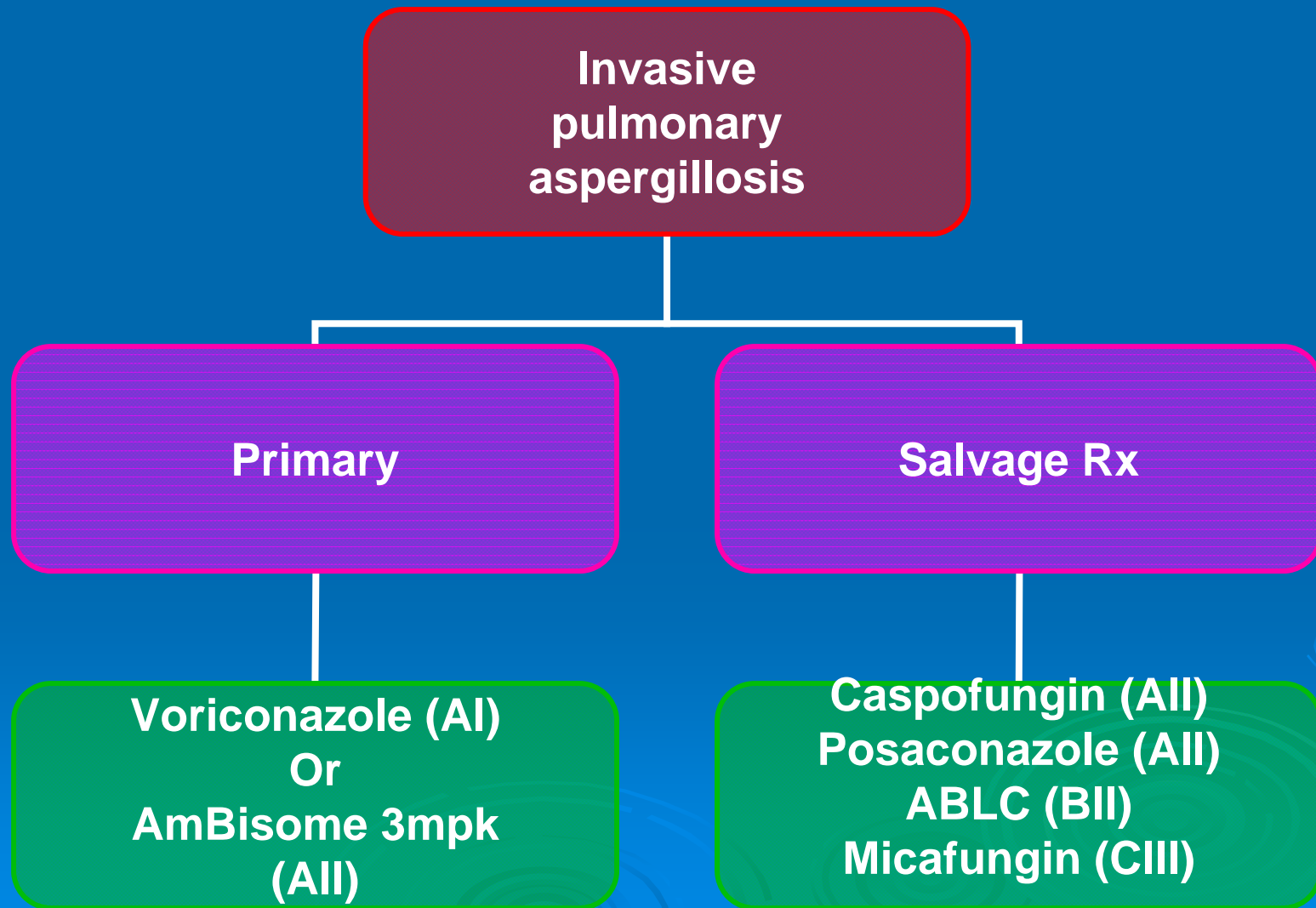


# Recommendations of the Australian ID Working Group Intern Med J 2008



# Recommendations of the German ID Working Party

## Ann Hematol Sept. 2008





4/15

*"Take these and phone me right away if they work."*

Thank you!

