Guidelines HAP/VAP

Standpoint from (some) academics

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- Both the US and EUR are presently striving for streamlining registration trials in the HAP/VAP setting
- The academia (especially IDSA) did publish position papers/comments, mainly for the FDA guidelines (issued 2 years ago).
- These points to consider are valid for both guidelines
- What are the main differences about?

Inclusion criteria 1

US (FDA)	EMEA	Comments
	Inclusion criteria	
Hospitalized within 48h or within 7d discharge	Hospitalized within 48h or within 7d discharge	idem
New infiltrate on chest Rx (3d party for Rx assessment)	New infiltrate on chest Rx	Idem
48 h "mechanical ventilation"	Intubated only (explicitely excludes NIV) and >48hrs	*Actually NIV pts are at increased risk of mortality*

Inclusion criteria 2

Evidence of septic ambiance: fever/hypothermia And Elevated WBC or leukopenia and clinical focus on respiratory tract (purulence expectoration/suction)	Clinical feature 3-4 among the following: cough, dyspnea, tachypnea, pleuritic pain, purulence, fever	Criteria less precise than FDA No mention of hypothermia; *What if normal temperature? FDA no; EMA Yes;* *What if no purulent secretion? FDA no; EMA yes* *NB: FDA Elevated PMN threshold criticized by academia*
HAP: Some clinical signs among: dyspnea tachypnea, cough or physical signs, or increase O2 needs (PaO2 <=60 sat <=90 PaO2/FIO2 "worsening") VAP: Some physical signs or increase O2 needs	increase O2 needs PaO2 <=60 sat <=90 PaO2/FIO2 "worsening" Physical signs at examination could be absent (no difference made HAP/VAP)	*Why not present signs/findings/anomalies along categories? would be helpful to figure out what are the patients about*

Exclusion criteria

FDA	**EMA**	comments
	Exclusion criteria	
	Exclude if pts seen only in emergency care	*excludes authentic HAP pts* • *what if seen in emergency care and stayed >48 hours?* • *what if seen in emergency and has pneumonia within 7 d of previous discharge ?*
No prior AB (<30 days); allowance for clinical failures, or non-related AB	Advice to "provide clear limitations" in the protocol	*FAD proposal criticized by academia (impact on recruitment); EMA wording (in #558) seems more flexible.*
Concomitant AB; specify which can be used, discontinue asap, monotherapy to end with.	Allusions to combination therapy, and request for details/conditions for reversion to monotherapy.	*EMA wording fuzzier. Importance of making out strategy trials (inadequate) from explanatory trials.*

Severity scores

FDA	EMA	Comments
	Severity scores	
Goal: anticipated mortality>=20%	Possibility to aim at > 10-20% and left optional (“may”)	*FDA option/”philosophy” more straightforward; EU has a fuzzier perspective*
Exclusion of population with a “good” severity score	Nothing explicit	*See above*
APACHEII, SOFA , MODS	APACHEII, SOFA , MODS	*idem*

Bacterial origin *(no magical solution)*

FDA	**EMA**	Comment
CPIS >= 6	CPIS >= 6	If only at enrolment can exclude 25% of pts (*require CPIS at Day 3 + microbiological data?)*
1ary population: only those with confirmed bacterial origin (mITT) Samples suggested (expectoration, deep tracheal aspirate, BAL/protected brush) Thresholds for colonies suggested Rapid tests and biomarkers alluded to	Requirement for bacterial origin left optional; If threshold used, plan stat analysis including pts excluded by too low thresholds (ITT as opposed as mITT) Rapid tests alluded to	*The European guidelines suggest that patients with diminished likelihood of bacterial origin be included.* *If mITT, make sure that this does not exclude more than 4-10% of pts, especially in NI trials.*
	Analysis along pathogens optional	*This can be only exploratory*

endpoints

	endpoints	
1ary: all cause mortality at 28 days	1ary "Clinical outcome" at TOC Day 14-21 acceptable; all cause mortality 28 ds 2ary; (proportion discharged, as 2ary)	*There is a wide discrepancy between the 2 guidelines*
Clinical/surrogates not recognized; otherwise, discuss early with agency	Clinical endpoints/surrogate markers: no details/guidance given	*This area is still in the making; no clear guidelines possible presently*
Non-inferiority margin less than to 10% (with computation, following thorough literature analysis, done in the appendix)	Non-inferiority margin up to 12,5%	*What basis for the 12,5% figure?* *Interest of relative margins with odds ratios?*

Methodology, number of trials

FDA	**EMA**	Comments
	design	
DB, RDZed	DB	idem
	Number of trials	
2 trials HAP or VAP; VAP can validate HAP, not the converse Trials separate for VAP and HAP	Idem; Provision for "mixed population" trials with 30% VAP?	*The EU proposal of mixed trials runs the risk of underpowering for both clinical and mortality endpoints. Clearly HAP and VAP patients are different*

safety

FDA	**EMA**	Comments
	safety	
Minimum % of pts >65yrs and renal impairment	No mention	*In general I would favor a HAP/VAP guideline standing on its own rather than just a few lines addendum*

conclusions

- The plan EU guidelines are at variance with the US ones on critical points:
  - Possibility of selection of patients with less severe disease (lower mortality)
  - Bacterial origin not part of the 1ary population (ITT vs mITT)
  - 1ary endpoint clinical outcome vs mortality
  - Inferiority margin 12,5 vs 10%
  - Possibility of mixed HAP/VAP populations in trials
- Quite a few academics more aligned on the IDSA standpoint, closer to the FDA one

Aim of the trial guidelines (and subsequent data analysis)

- Try to avoid approval of sub-optimal drugs (especially in Non-inferiority trials)
  - In patients where underlying severity factors raise the threshold for effectiveness (e.g. doripenem, tigecycline, ceftobiprole)
- Try to limit the risk of undetected increase in iatrogenicity, diluted because of sample sizes
  - (e.g. excess death for tigecyclin)
- Help to put on the market drugs that are effective on the right bugs, (among which those from the ESKAPE family), drugs to be actually « stress-tested » during the drug development process
- Have a single set of rules on both sides of the Atlantic: wouldn't that facilitate drug development?