EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Requirements for approval of new antibacterials in the EU

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Current EU regulatory requirements for the approval of a new antibacterial

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19 May 2022
CPMP/EWP/558/95 Rev 3
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections

Draft agreed by Infectious Disease Working Party	September 2018
Adopted by CHMP for release for consultation	13 December 2018
Start of public consultation	19 December 2018
End of consultation (deadline for comments)	31 July 2019
Agreed by Infectious Disease Working Party	December 2019
Adopted by CHMP	19 May 2022
Date of coming into effect	1 December 2022

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-medicinal-products-indicated-treatment-bacterial-infections-revision-3_en.pdf

Non-clinical assessment of antibacterial activity-microbiology

- Spectrum of antibacterial activity
  - Need to elucidate the mechanism of action of **new** antibacterial agents
  - $MIC_{50,}$ $MIC_{90,}$ and MIC range presented by species and by subgroup (with/without resistance)
  - against clinical isolates obtained within 5 years prior to filing an application dossier (10-hundreds)
  - metabolites and their activity to be assessed separately
  - Need to estimate rate of resistance at time of approval
- For combinations: in vitro susceptibility testing results should support use of combination compared to each agent alone (against non-resistant and resistant pathogens)
  - Risk of resistance selection lower with combination
  - Determine ratio to be further tested in NC/C studies
  - New BLI:
    - investigate mechanism of inhibition
    - Document if any intrinsic antibacterial activity at clinical concentration
    - Test BL/BLI against strains resistant to BL alone →fixed BLI concentration or fixed BL:BLI ratio

Non-clinical assessment of antibacterial activity-microbiology/other

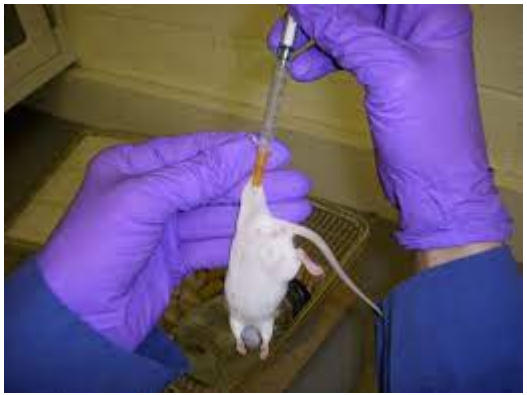
- Investigate mechanisms of resistance for pathogens with high MICs
  - If candidate from a new class investigate potential for cross-resistance
  - If from a known class investigate cross-resistance within the class
- Also investigate risk of selecting resistance in an *in vitro* PD model

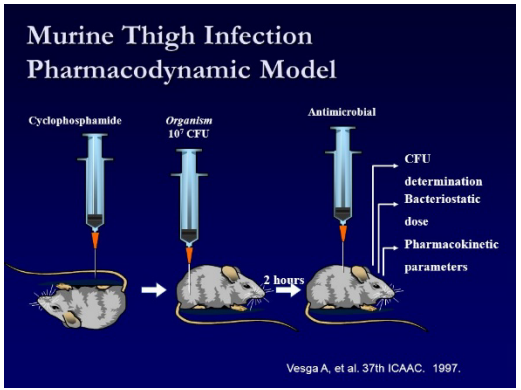
Other *in vitro* studies:

- Determine MBC
- Conduct time-kill studies with relevant species/resistant organisms →relationship between test agent concentration and antimicrobial activity
- Investigate synergy/antagonism/PAE

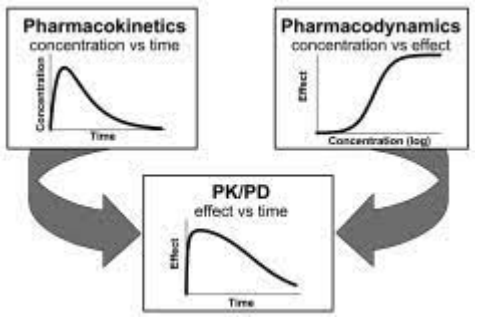
Non-clinical assessment of antibacterial activity-*in vivo* studies

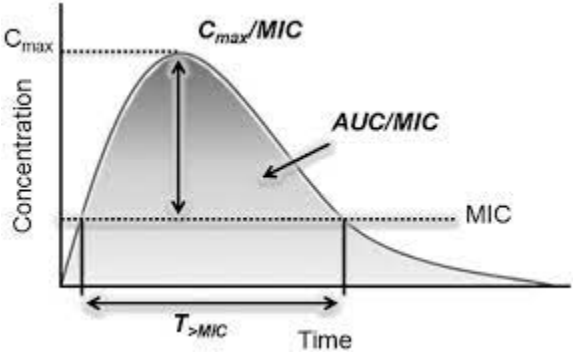
- If appropriate non-clinical models exist (relevant to the intended clinical use)→evaluation of efficacy of the test agent against the most likely causative pathogens



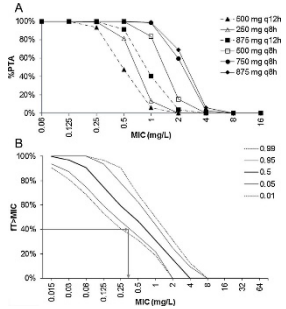


PK/PD analyses





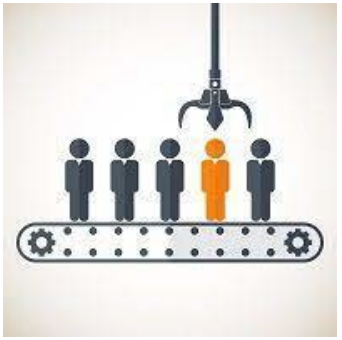
- Support dose regimen selection
- Inform clinical breakpoints selection
- PK/PD indices may be identified from in-vitro and/or in-vivo PD models
- Nonclinical PD targets (PDTs) should be established for the most important pathogens
- determination of the probability of target attainment (PTA)
  - using simulations to support dose regimen selection
  - requires adequate clinical PK data and the use of population PK (popPK) models.
- clinical exposure-response (E-R) relationships and their use to derive clinical PDTs



Clinical programmes

Patient Selection

- Use rapid diagnostic tests to maximize patients with a culture-confirmed pathogen
- Use rapid susceptibility tests if available
- 24h of prior antibacterial therapy allowed



Causative pathogens

- Baseline specimens/culture/serology or within 12/24 h after randomisation
- Confirmation by culture (other methods subject to assessment of justification)
- List acceptable causative pathogens in the protocol

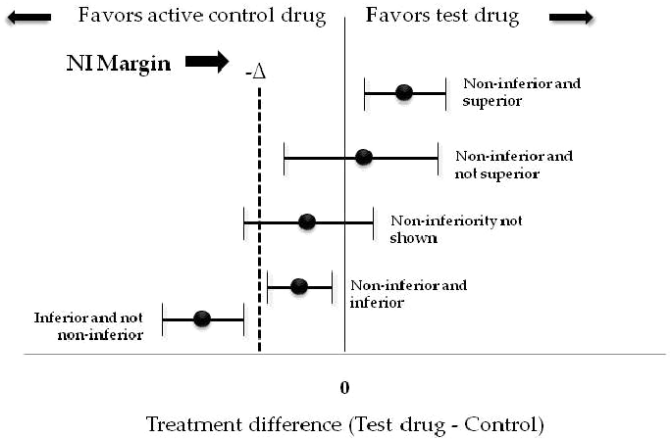
	Major community-based pat
	Streptococcus pneumoniae *Haemophilus influenzae* *Legionella* spp. *Chlamydia pneumoniae*
	Escherichia coli *Bacteroides fragilis*
	Streptococcus pyogenes *Staphylococcus aureus* Polymicrobial
	Escherichia coli *Klebsiella* spp. *Enterobacter* spp. *Proteus* spp. VRE

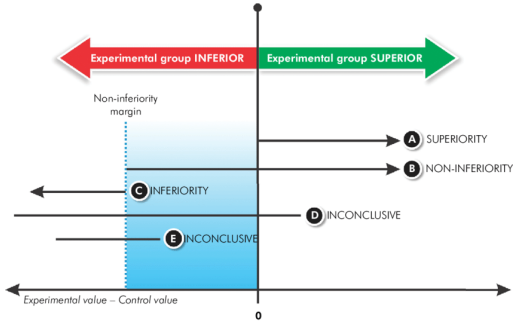
Dose regimens

- PK/PD analyses support the dose regimen to be tested
- Cannot be used to select dose regimen in the case of antibacterial formulations that exert local effect (e.g. topical, inhalational and intra-gut antibacterial activity)→ dose-finding study
- Cannot define treatment duration→ treatment guidelines and PK data
- Risk of resistance selection! → use in vitro PD models

Efficacy trial designs-NI trials

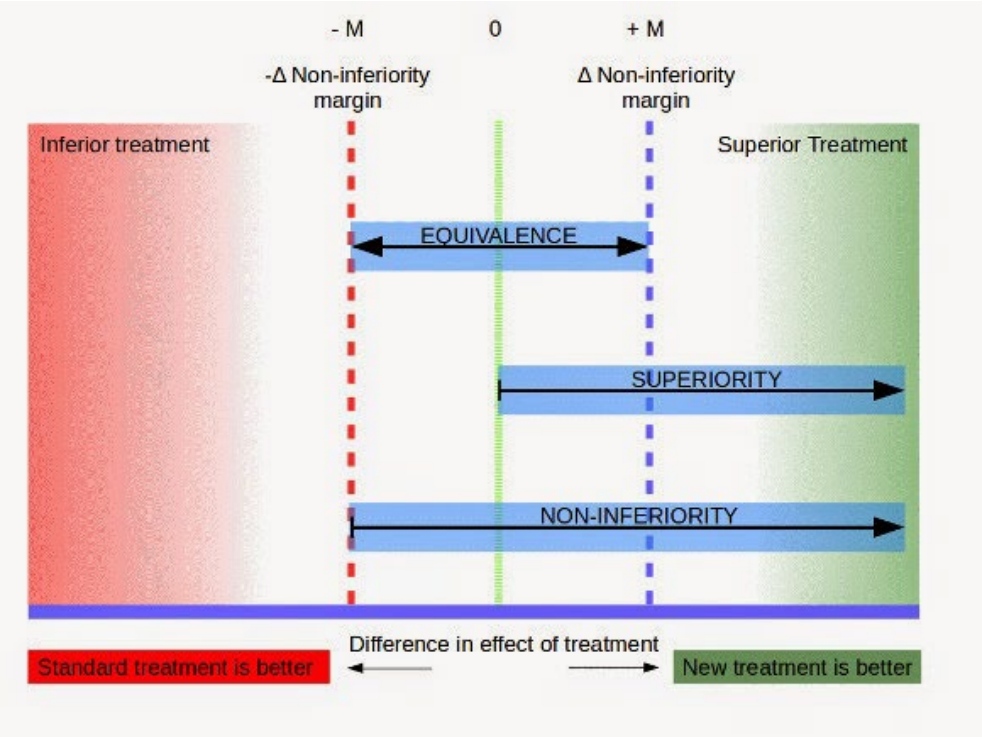
- Acceptable when:
  - Licensed treatment available
  - Magnitude of treatment effect versus placebo known
- Selection of non-inferiority margin
  - the need to indirectly demonstrate the no-treatment effect
  - How large a difference between the text agent and the reference drug can be clinically important
  - For major indications suggestions are made
- Choice of comparator (including dose and duration of treatment)
  - Critical to overall validity
  - Best available therapy, normally licensed in the EU
  - A single comparative regimen is preferred





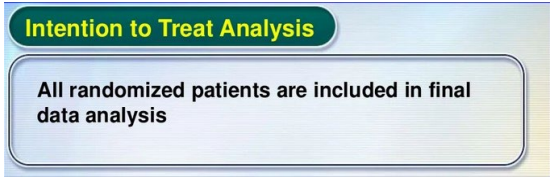
Efficacy trial designs-superiority trials

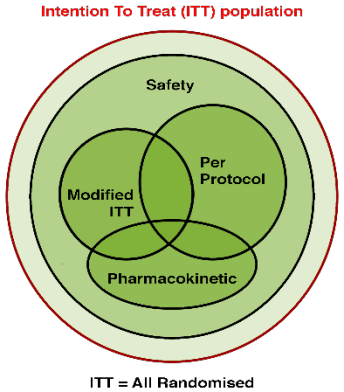
- required when:
  - no licensed treatment/ standard of care treatment available or
  - the treatment effect of the licensed treatment/ standard of care treatment is unknown/ questionable
- superiority over placebo desirable when infection is self-limiting/of short duration



Analyses of efficacy

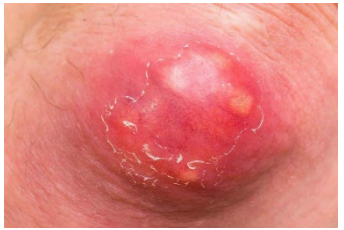
- Primary analyses
  - Clinical primary endpoint: all randomised (ITT) population
  - Microbiological or microbiological/clinical primary endpoint: microbiological-ITT population
- Secondary analyses-conduct in:
  - All randomised patients who received at least one dose of assigned treatment and the subset of this population with a relevant pathogen);
  - The clinically evaluable population, including patients who meet the inclusion criteria and have adhered to the protocol and assigned treatment, and the microbiologically evaluable population (subset of the clinically evaluable population with a relevant pathogen
  - Other pre-defined sub-populations that may be of interest

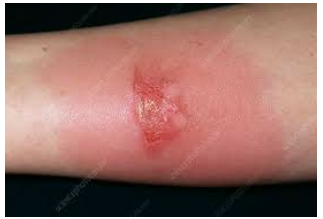


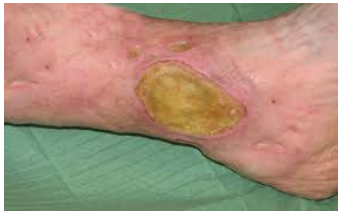


Non-inferiority trials to support specific indications

- Acute bacterial skin and skin structure infections (ABSSSI)
  - Acceptable types of infection for study: cellulitis, erysipelas, wound infections and major abscesses
  - The protocol should set a limit on the proportion of patients with burns that are enrolled
  - The proportion of patients enrolled with abscess should be limited (e.g. up to approximately 30% of the total patients)
  - Window (e.g. 24-48h) is specified around the time of randomisation
  - Patients should demonstrate a protocol-defined minimum number of signs and symptoms associated with an ongoing acute infectious process
  - Exclude patients with suspected or confirmed osteomyelitis or septic arthritis and those with severe necrotising infections that require specific surgical and pharmacological management
  - Clinical outcome in the ITT population at TOC visit timed from randomisation; 7-14 days post end therapy (primary endpoint);
  - non-inferiority margin is -10%



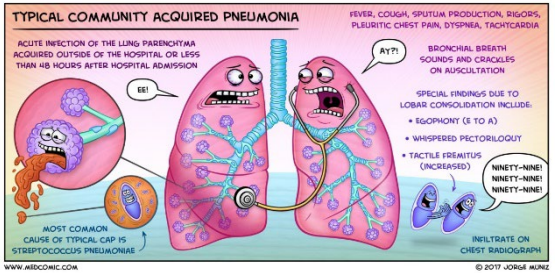


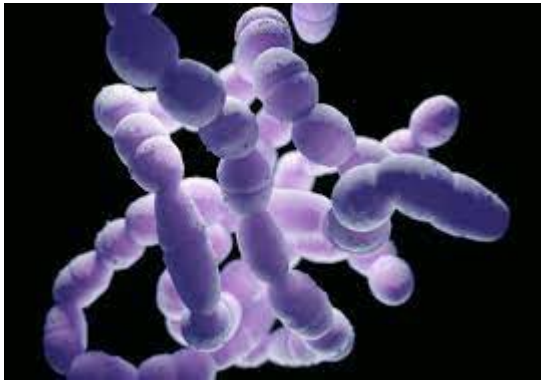


Non-inferiority trials to support specific indications

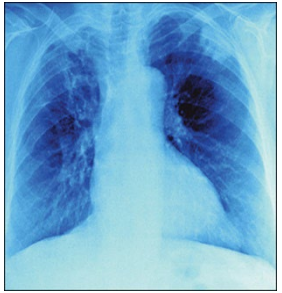
- Community-acquired pneumonia (CAP)

  - chest radiograph within 48h prior to enrolment: new lobar/multilobar infiltrates
  - Patients should present min 3-4 from: new onset cough, purulent sputum, fever, dyspnoea, tachypnoea and pleuritic chest pain and at least 1: percussion/auscultation
  - IV patients: minimum PORT scores of III and IV-V (at least 25%);
  - PO patients: PORT scores of II and III (at least 50%) at the time of randomization
  - Stratification of enrolment: age <65 years and ≥65 years and no upper age limit
  - Exclusion of patients with pneumonia secondary to aspiration/obstruction, cystic fibrosis
  - Primary endpoint: clinical outcome in the ITT population at TOC visit timed from randomisation;
  - 5-10 days post end therapy (primary endpoint);
  - Non-inferiority margin: -10%





Non-inferiority trials to support specific indications



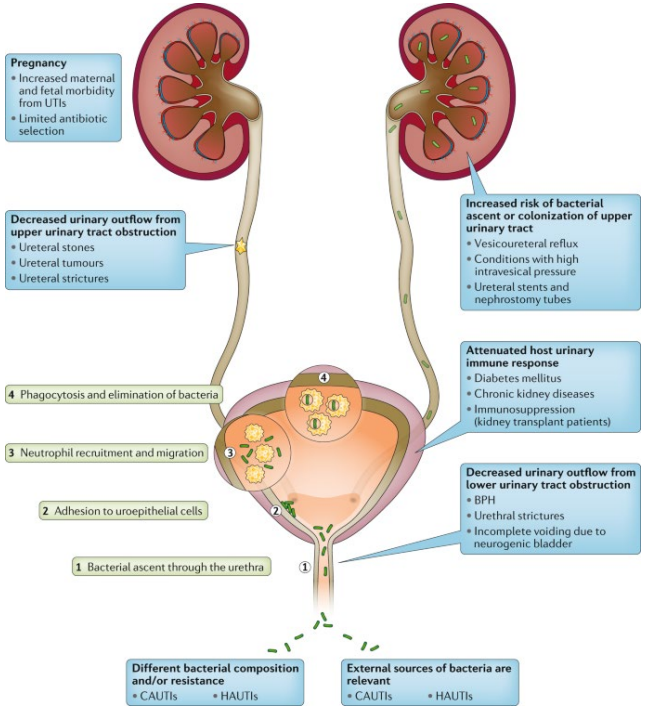
- Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP)
  - Demonstration of efficacy in VAP could support an indication that includes HAP but not vice versa
  - Ensure that representative samples of patients in each category are enrolled (e.g. at least 25-30% should have VAP)
  - HAP patients should have been hospitalised for 48h before first signs/symptoms; minimum number of clinical features; new infiltrate on chest radiograph
  - VAP patients should have received mechanical ventilation for 48h
  - Primary analysis: clinical outcome in the ITT population at TOC visit timed from randomisation;
  - non-inferiority margin is -12.5%
  - all-cause mortality and patients that are discharged from hospital within a pre-specified

    post-randomisation follow-up period (secondary endpoint)

Non-inferiority trials to support specific indications

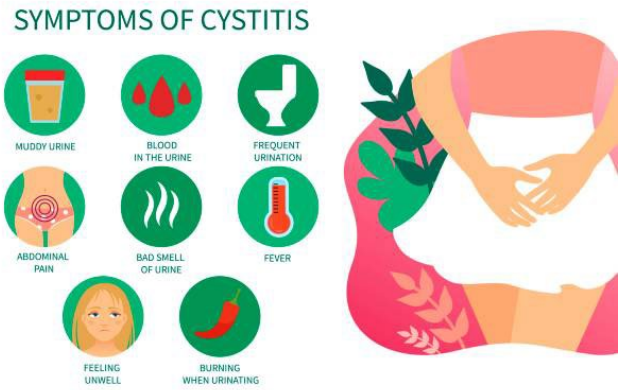
- Complicated urinary tract infections (cUTI) and acute pyelonephritis (AP)

  - Patients with at least one of indwelling urethral catheter, urinary retention, urinary obstruction or neurogenic bladder;
  - Exclude patients with ileal loops or vesico-ureteric reflux and patients with signs/symptoms of prostatitis
  - If AP and cUTI patients in the same study, at least 30% of patients with AP
  - Patients eligible for microbiological-ITT population need >1×10^5 CFU/mL of a single, or max 2 relevant pathogens
  - Primary analysis: combined clinical and microbiological (<1×10^3 CFU/mL) success rate in the microbiological-ITT population at TOC visit timed from randomisation;
  - non-inferiority margin is -10%



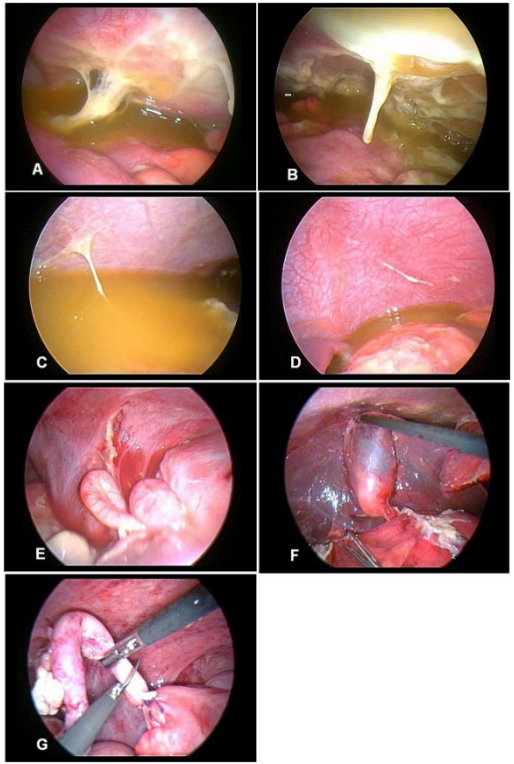
Non-inferiority trials to support specific indications

- Uncomplicated urinary tract infections (uUTI)
  - Female patients with acute cystitis (min number of symptoms; e.g. frequency, urgency, dysuria)
  - Enrolment of patients before microbiological culture results available on documented pyuria (≥10 WBCs/mm3)
  - Patients eligible for microbiological-MITT need >1×10^5 CFU/mL of a single relevant pathogen in the baseline urine sample
  - Primary analysis: combined clinical and microbiological success (cUTI) in microbiological-ITT population at TOC;
  - non-inferiority margin -10%



Non-inferiority trials to support specific indications

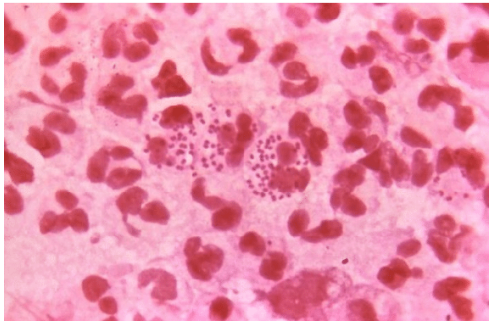
- Complicated intra-abdominal infection (cIAI)
  - Patients with diagnosed cIAI during laparoscopy, laparotomy or percutaneous drainage
  - Patients with infections originating in the appendix max 50%
  - Stratification at randomisation according to appendix and non-appendix-associated cIAI
  - Exclusion of patients with perforations of the stomach and small intestine, unless evidence of a secondary infection process within the abdominal cavity
  - Clinical outcome in the microbiological-ITT at TOC visit
  - non-inferiority margin is -12.5%→ -10%



doi: 10.1016/j.ijscr.2020.05.089

Non-inferiority trials to support specific indications

- Uncomplicated gonorrhoea
  - Patients with evidence of gonococcal cervicitis or urethritis at enrolment: Gram-negative diplococci and positive culture results for *N.gonorrhoeae* (microbiological-MITT population)
  - Stratification by infection site at randomisation in case of enrolment of patients with rectal or pharyngeal gonorrhoea (alone or in conjugation with urethral or cervical infection)
  - TOC visit within one week (e.g. 3-4 days) after treatment
  - Primary analysis: microbiological eradication in the microbiological-ITT population at TOC;
  - non-inferiority margin -10%

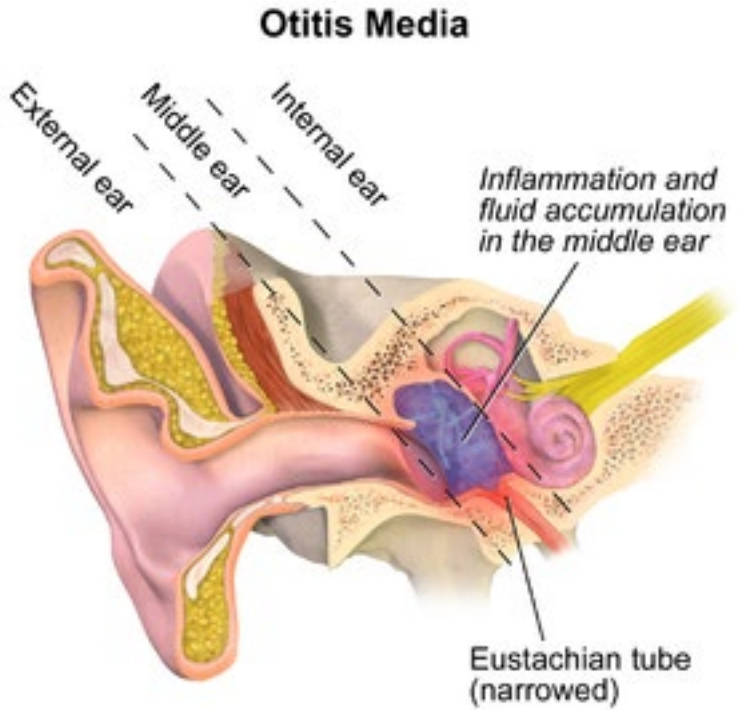


Cervicitis in a woman with gonorrhea

Reproduced from: Sexually Transmitted Diseases: STD Clinical Slides. Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/std/training/clinicalslides/slides-dl.htm (Accessed on April 24, 2014).

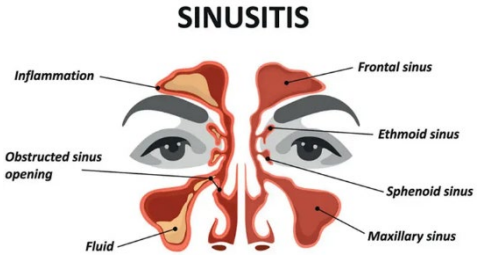
Superiority trials to support infection site-specific indications

- Acute otitis media (AOM)
  - Trials in AOM are feasible only in children
  - In children 6 months to 3 years of age: NI trial is feasible
  - All other age groups need superiority trials for approval

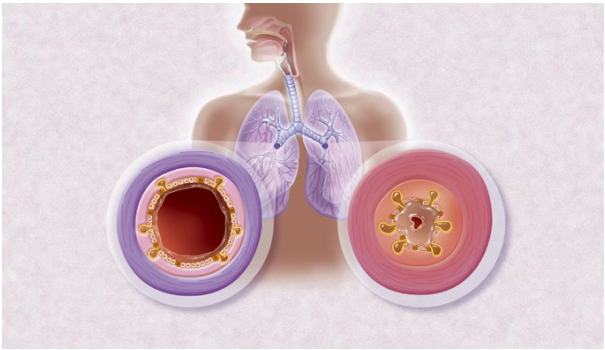


Superiority trials to support infection site-specific indications

- Acute bacterial sinusitis (ABS)
  - At least one trial required in patients with maxillary sinusitis
  - Primary analysis based on clinical success in microbiological-ITT population;
  - Primary endpoint: resolution of clinical signs and symptoms at TOC visit

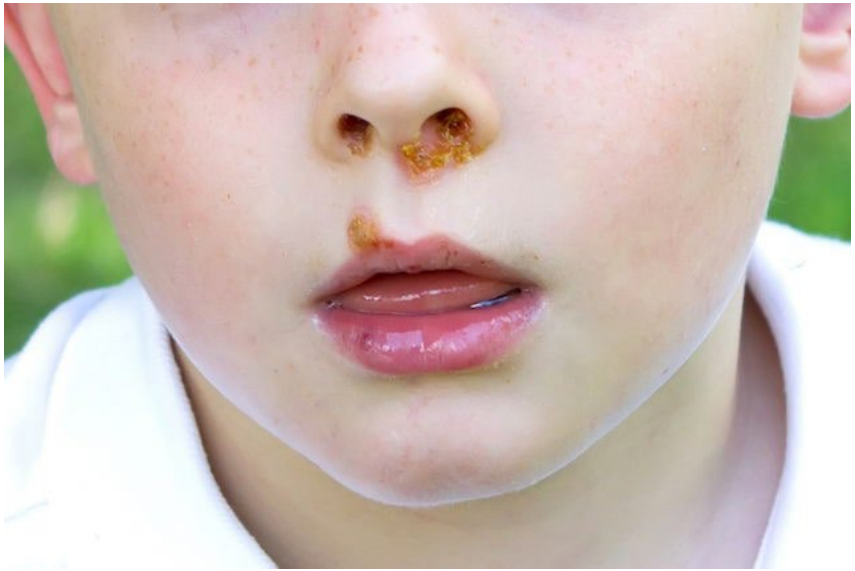


- Acute bacterial exacerbations of chromic bronchitis (ABECB or non-cystic fibrosis bronchiectasis (NCFBE)
  - Patients with exacerbations requiring antibacterial therapy meeting recognised criteria
  - Primary analysis based on clinical success in ITT-population;
  - Clinical success= resolution of signs and symptoms of exacerbation and/or return to baseline status



Superiority trials to support infection site-specific indications

- Superficial skin infections
  - Separate studies for impetigo, superficial wound infections and infected dermatoses
  - Limitations regarding the use of adjunctive therapies (e.g. antiseptics and topical corticosteroids)
  - Primary endpoint: resolution of signs and symptoms of infection at a TOC visit in the microbiological-ITT population;
  - time to resolution of the infection (assessed at EOT) may be acceptable as primary when treating infections with high spontaneous resolution rates



Circumstances in which limited clinical data may be accepted

- Antibacterial agents that treat infections due to MDR organisms that are currently uncommon or rare and for which there are a few therapeutic options
- Antibacterial agents with a very narrow antibacterial spectrum of activity
- A new antibacterial agent in a new class that has a unique mechanism of action (new target)
- New agents of existing classes that are active against other members of the same class
- New or known antibacterial agents of existing class coupled with new protective agent (beta-lactam/beta-lactamase inhibitor)

Eligibility for accepting limited clinical data

- In-vitro studies
  - New class: demonstration that MICs are unaffected against species resistant to most/all licensed antibacterial agents
  - Existing class: demonstrate no important difference in MICs between organisms resistant (or not) to other agents in the same class
- PK-PD analyses: critically important!
  - Support the clinical dose regimen sufficient to treat MDR organisms
  - Support anticipated efficacy against ‘‘target’’ MDR pathogens
  - PK data are essential
- Clinical trials
  - Conduct at least one randomised comparative trial, if possible, in a single appropriate indication
  - Should enable the drug to be evaluated as monotherapy against species within its antibacterial spectrum of activity
  - If trial is intended to support a pathogen-specific indication, no need to meet non-inferiority margins

Any questions?

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