Καταληκτικό σημείο κλινικής δοκιμής για λοιμώξεις ουροποιητικού:
διαφορές με την καθημερινή πρακτική

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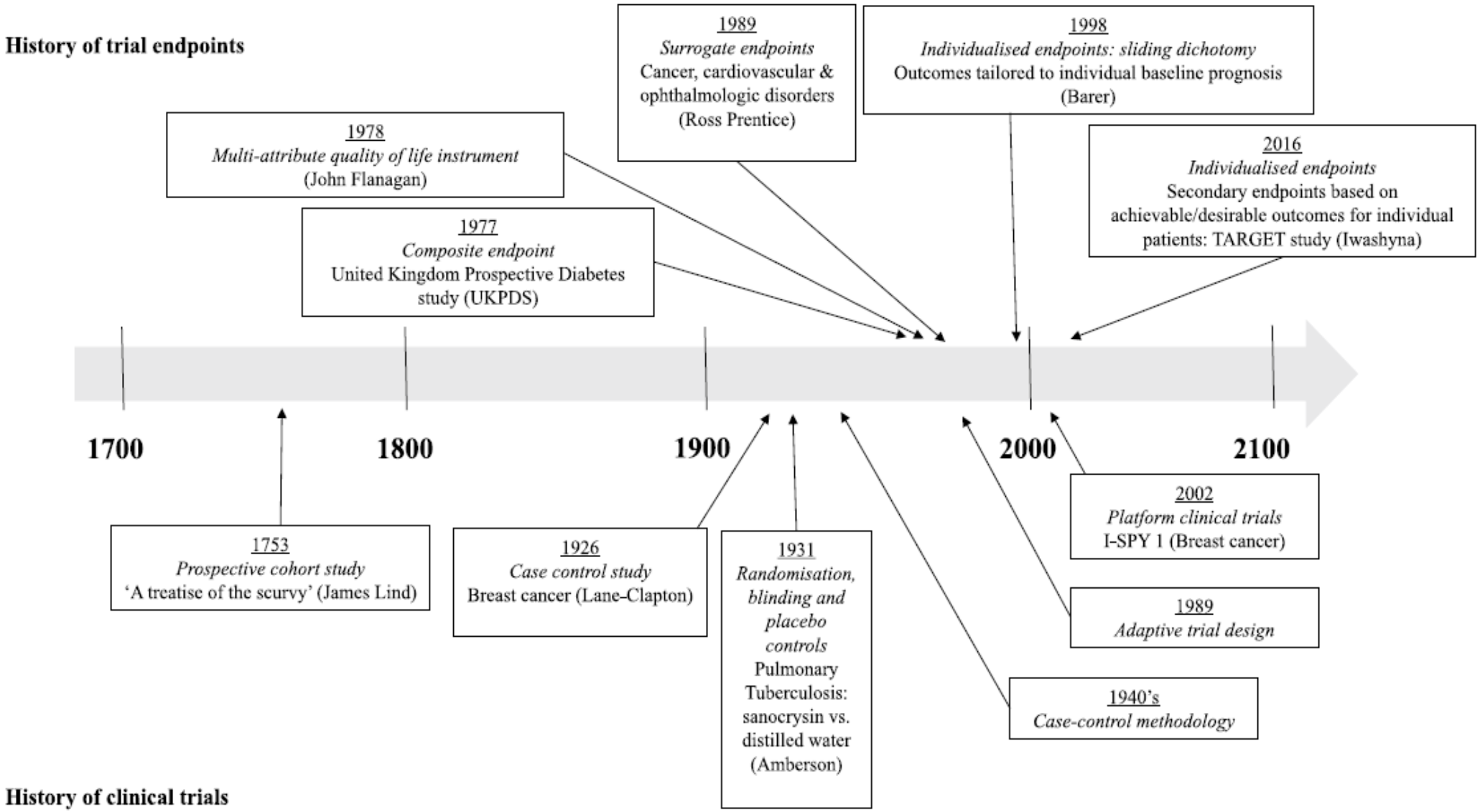


Fig. 2. Evolution of clinical trials and historical use of endpoints.

McLeod C et al. Clinical Trials Communication 2019; 100486.

Σκοπός της έρευνας

- Οι υποθέσεις είναι εικασίες για τη σχέση έκθεσης – νόσου που οδηγούν σε μαχητές προβλέψεις
  - Π.χ. Η χορήγηση αντιμικροβιακής αγωγής σε ασυμπτωματική βακτηριουρία μειώνει τον κίνδυνο εμφάνισης σοβαρής συμπτωματικής λοίμωξης από το ουροποιητικό

- Ποια είναι η πρωτογενής έκβαση;
- Τι είδους έρευνα πρέπει να διενεργηθεί;
- Ποια είναι η προέλευση του πληθυσμού που θα ερευνηθεί, η διαδικασία επιλογής των συμμετεχόντων, το μέγεθος του δείγματος και αν χρειάζεται ομάδα ελέγχου και το πηλίκο μελετώμενων περιπτώσεων προς ομάδα ελέγχου
- Είναι δυνατή η ύπαρξη συστηματικού σφάλματος στην επιλογή των συμμετεχόντων της έρευνας;

Κλινικές μελέτες

Purpose of clinical trials

To generate evidence to guide decision-making in clinical practice and in policy

Randomized clinical trials represent the gold standard for generating evidence

- Outcomes selected must address the trial objectives
- Endpoints are the specific measures of these outcomes
- Primary endpoints are efficacy measures that address the main research question
- Secondary endpoints are not sufficient to influence decision-making alone, but may support the claim of efficacy by demonstrating additional effects or by supporting causal mechanism

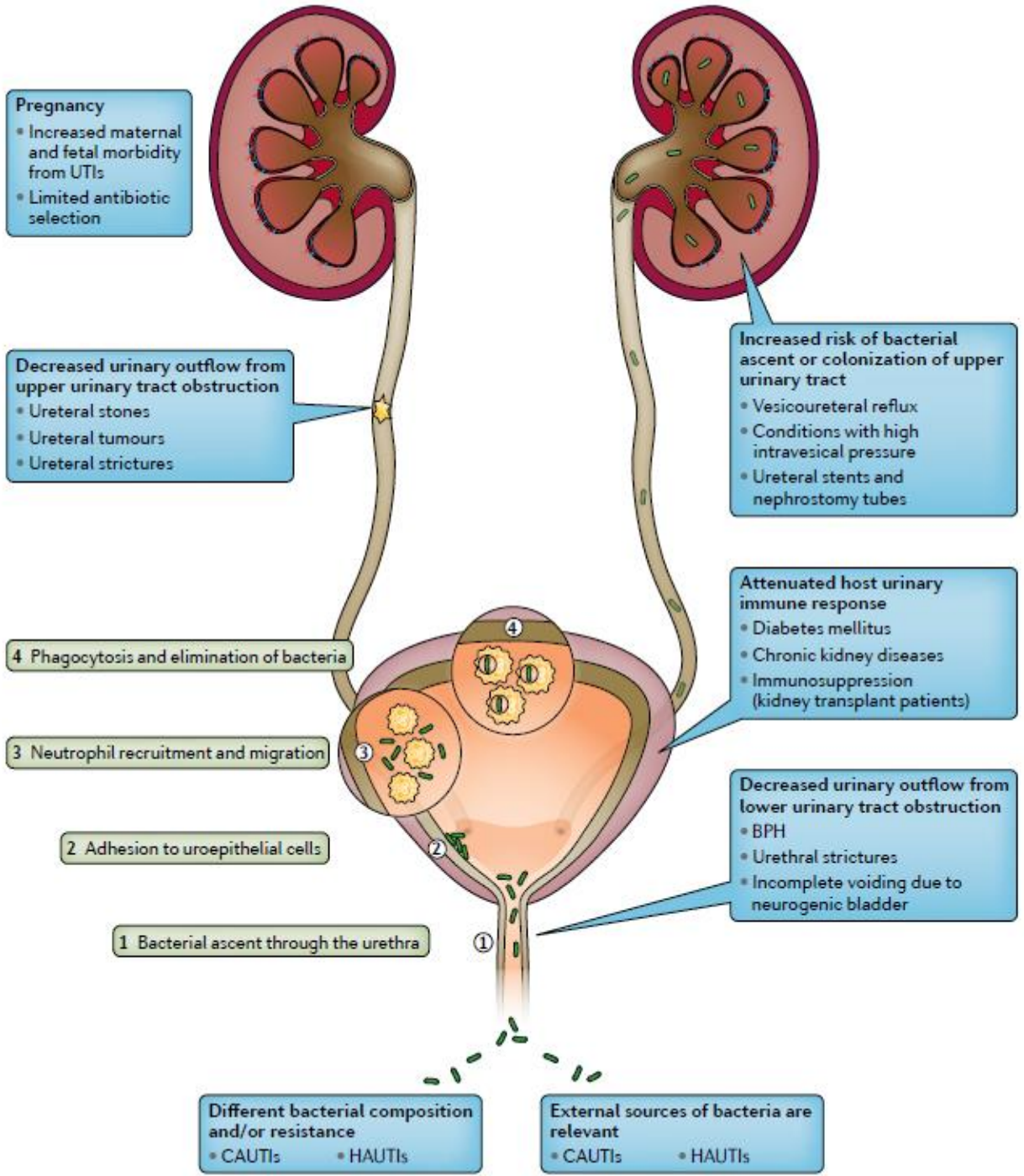
Τρόποι αξιολόγησης της θεραπευτικής αποτελεσματικότητας

- Έρευνες απλής κλινικής παρακολούθησης χωρίς συγκριτικό δείγμα
- Διαχρονικές πληθυσμιακές συγκρίσεις σε συνάρτηση με την εφαρμογή ενός νέου θεραπευτικού μέτρου (time trends)
- Συγκριτικές κλινικές μελέτες χωρίς τυχαιοποίηση
- Τυχαιοποιημένες και ελεγχόμενες έρευνες θεραπευτικής παρέμβασης

Ταξινόμηση

- **Κατώτερου ουροποιητικού:**
  - Ουρηθρίτιδα
  - Κυστίτιδα
  - Προστατίτιδα

- **Ανώτερου ουροποιητικού:**
  - Οξεία πυελονεφρίτιδα
  - Ενδονεφρικό και περινεφρικό απόστημα


Pregnancy
• Increased maternal and fetal morbidity from UTIs
• Limited antibiotic selection
Decreased urinary outflow from upper urinary tract obstruction
• Ureteral stones
• Ureteral tumours
• Ureteral strictures
Increased risk of bacterial ascent or colonization of upper urinary tract
• Vesicoureteral reflux
• Conditions with high intravesical pressure
• Ureteral stents and nephrostomy tubes
Attenuated host urinary immune response
• Diabetes mellitus
• Chronic kidney diseases
• Immunosuppression (kidney transplant patients)
4 Phagocytosis and elimination of bacteria
3 Neutrophil recruitment and migration
2 Adhesion to uroepithelial cells
1 Bacterial ascent through the urethra
Decreased urinary outflow from lower urinary tract obstruction
• BPH
• Urethral strictures
• Incomplete voiding due to neurogenic bladder
Different bacterial composition and/or resistance
• CAUTIs • HAUTIs
External sources of bacteria are relevant
• CAUTIs • HAUTIs

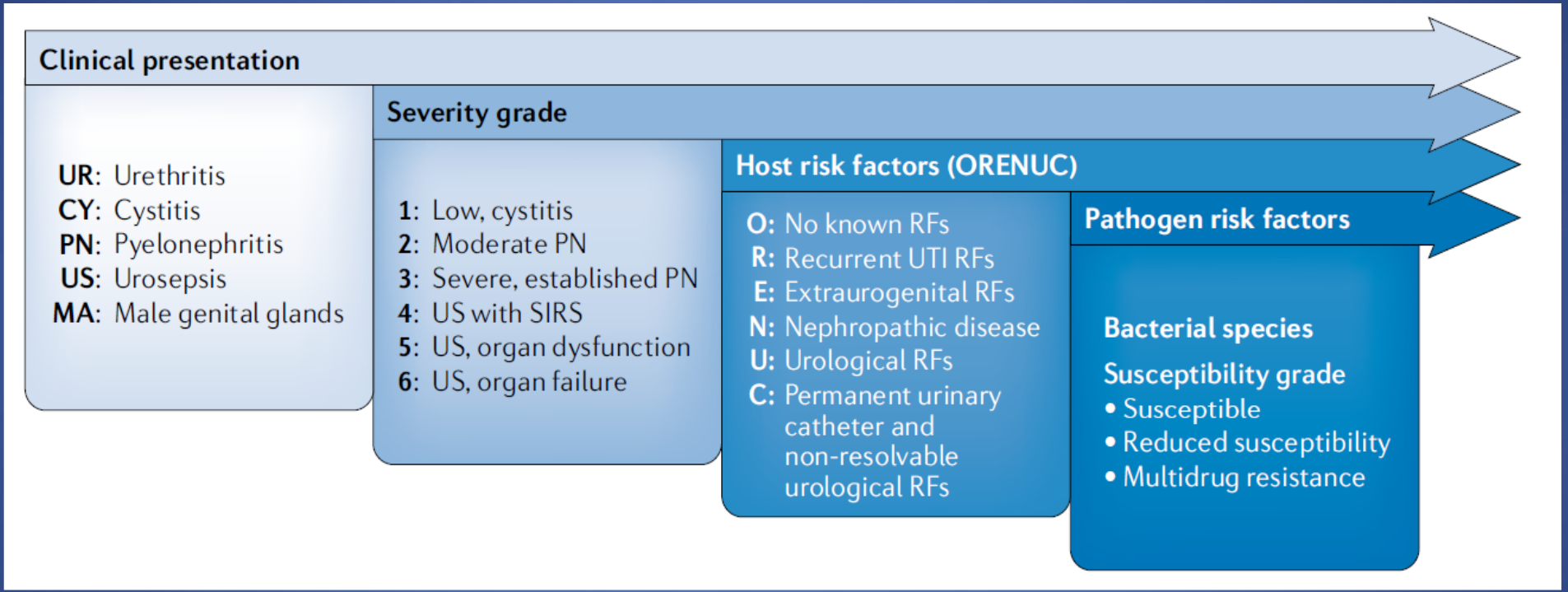
Ορισμοί

- **Μη επιπεπλεγμένη ουρολοίμωξη** : η ουρολοίμωξη σε υγιείς, μη έγκυες γυναίκες χωρίς πρόβλημα από το ουροποιητικό σύστημα
- **Επιπεπλεγμένη ουρολοίμωξη** : σε άνδρες ή παιδιά, σε λειτουργική ή ανατομική διαταραχή του ουροποιητικού συστήματος αυξημένο κίνδυνο επιπλοκών ή αποτυχίας της θεραπείας

Αίτια επιπεπλεγμένης ουρολοίμωξης

- **Ανατομικές ή λειτουργικές ανωμαλίες του ουροποιητικού**
- Υπερτροφία προστάτη, απόφραξη, λιθίαση, νευρολογικά νοσήματα, κυστεουρητηρική παλινδρόμηση, διαταραχή νεφρικής λειτουργίας
- **Χειρισμοί στο ουροποιητικό**
- Ουροκαθετήρας, νεφροστομία, pig-tail
- **Υποκείμενα νοσήματα**
- ΣΔ, ανοσοκαταστολή, δρεπανοκυτταρική αναιμία
- **Κύηση**
- **Άνδρες (>95%)**
- **Ηλικιωμένοι**
- **Παιδιά**

ORENUC classification



European Section of Infections in Urology , 2010

Συμπτώματα UTI

Table 1 | **Classical symptoms of different UTI entities**

Acronym	Clinical diagnosis	Clinical symptoms	Severity grade
CY-1	Cystitis	Dysuria, frequency, urgency, suprapubic pain; sometimes unspecific symptoms	1
PN-2	Mild to moderate pyelonephritis	Fever, flank pain[a], CVA tenderness[a]; sometimes unspecific symptoms with or without symptoms of cystitis	2
PN-3	Severe pyelonephritis	As for PN-2, but, in addition, nausea and vomiting with or without symptoms of cystitis	3
US-4[b]	SIRS	Temperature >38 °C or <36 °C, heart rate >90 beats/min, respiratory rate >20 breaths/min or $PaCO_2$ <32 mm Hg (<4.3 kPa), WBCs >12,000 cells/mm^3 or <4,000 cells/mm^3 or ≤10% immature (band) forms with or without symptoms of cystitis or pyelonephritis (>2 SIRS criteria must be met for US-4 diagnosis)	4
US-5[b]	Severe urosepsis	As for US-4, as well as organ dysfunction, hypoperfusion or hypotension; hypoperfusion and perfusion abnormalities may include but are not limited to lactic acidosis, oliguria or an acute change in mental status	5
US-6[b]	Uroseptic shock	As for US-4 or US-5, as well as hypotension despite adequate fluid resuscitation and the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria or an acute change in mental status; patients who are on inotropic or vasopressor agents may not be hypotensive when perfusion abnormalities are measured	6

ΟΞΕΙΑ ΜΗ ΕΠΙΠΕΠΛΕΓΜΕΝΗ ΠΥΕΛΟΝΕΦΡΙΤΙΔΑ

ΠΡΟΤΕΙΝΟΜΕΝΑ ΘΕΡΑΠΕΥΤΙΚΑ ΣΧΗΜΑΤΑ ΓΙΑ ΑΓΩΓΗ ΚΑΤ'ΟΙΚΟΝ

IDSA *Clin Infect Dis* 2011; 52: e103-e120

Αντιμικροβιακό	Δόση	Διάρκεια
Σιπροφλοξασίνη	500 mg x 2 από του στόματος	7 ημέρες
Λεβοφλοξασίνη	750 mg x 1 από του στόματος	5 -7 ημέρες
Κοτριμοξαζόλη (με αντιβιόγραμμα)	960 mg x 2 από του στόματος	14 ημέρες
Κεφουροξίμη	500 mg x 2 από του στόματος	10-14 ημέρες
Αμοξυκιλίνη-κλαβουλανικό	1 gr x 2 από του στόματος	10-14 ημέρες
Κεφτριαξόνη	2 gr x 1 ενδομυικά	Αρχικά (3ημέρες) ως αντιβιογράμματος
Αμινογλυκοσίδη	Νετιλμικίνη 300 mg x 1 ή Αμικασίνη 1 gr x 1 (ενδομυικά)	Αρχικά (3 ημέρες) ως αντιβιογράμματος

Endpoints, clinical and non-clinical

- **Clinical endpoints:**

-Reported by clinicians (ClinRO) and involves judgement or interpretation of clinical signs or events

-Assessed by standardized performance measures

-Patient reported (PRO)

-Observer-reported (ObsRO)

- **Non-clinical endpoints:** objectively measured indicators of a biological or pathogenic process (pharmacological response to a treatment intervention)=blood tests, fluid analyses, physiological measures

Η οργάνωση μιας συγκριτικής θεραπευτικής έρευνας

- Καθορισμός της θεραπείας που θα αξιολογηθεί
- Επιλογή των ασθενών
- Οι παρατηρήσεις σχετικά με το νόσημα
- Η κατανομή των ασθενών στις συγκεκριμένες ομάδες
- Το συγκριτικό δείγμα
- Ο αναγκαίος αριθμός ασθενών:

1) ο βαθμός στατιστικής σημαντικότητας 2) Ο βαθμός επιδιωκόμενης βεβαιότητας 3) η αποτελεσματικότητα του συγκριτικού θεραπευτικού μέτρου 4) η προβλεπόμενη αποτελεσματικότητα του θεραπευτικού μέτρου που δοκιμάζεται 5) το ποσοστό των ασθενών που χάνονται στην παρακολούθηση 6) ο ερευνητικός σχεδιασμός

Η οργάνωση μιας συγκριτικής θεραπευτικής έρευνας

- Η εξουδετέρωση των υποκειμενικών παραγόντων – τυφλός έλεγχος
- Η παρακολούθηση των ασθενών
- Το θεραπευτικό αποτέλεσμα

A superiority trial	A RCT designed to test whether a new treatment is better than an old treatment with respect to a pre-specified primary endpoint
A non-inferiority trial	A RCT designed to test whether a new treatment is at least as good as the active control, which often consists of the best available treatment at that moment in time. The main goal is to find therapies with advantages in other aspects, like the safety profile, administration method, or expense
Non-inferiority margin	A pre-specified, maximum treatment difference for the primary outcome measure that is still acceptable given the possible advantages of the new treatment
Attributable mortality	The mortality in the exposed study population minus the mortality in the unexposed study population; i.e. the mortality associated with the exposure, for example VAP
Composite endpoint	An endpoint combining multiple single endpoints into one measure, often including a clinical endpoint and a safety endpoint. This increases the power of the RCT, as compared to a RCT where both endpoints would be tested separately. For example, combining mortality and kidney failure, whereby the first occurrence of either is considered a negative outcome
Hierarchical endpoint	A special type of composite endpoint, whereby the hierarchy of the individual endpoints is considered; if the most important endpoint occurs, the other endpoints lower in hierarchy are no longer considered
Hierarchical nested design	A RCT design, where the primary endpoint needs to be compared in a non-inferiority design, and if non-inferiority is confirmed, predetermined additional endpoints can be tested for superiority
Competing events	An event that either hinders the observation of the event of interest or modifies the chance that this event occurs, i.e. hospital discharge in case hospital mortality is the primary endpoint
Multistate model	A statistical method to model an ongoing random process, thereby allowing patients to move from one state to a predetermined number of other states, for example from hospitalized to infected to death, whereby all transitions can be quantified

Timsit JF et al. Intensive Care Med 2017

Endpoint	Advantages	Disadvantages
All-cause mortality [23]	Robustness: highly objective, accurate, and simple to measure Important to patients Non inferiority design allowed	Requires large sample sizes or large differences between groups Highly dependent on patient severity A substantial part is not related to infection in critically ill patients Ideal assessment time-point is debatable Recommended non-inferiority margins are high from a clinical perspective
Attributable mortality [18]	More relevant than all-cause mortality if many other causes of death or comorbidities are present	As above plus: Very difficult to assess Limited objectivity and reproducibility
Quality of life/functional status [43]	Patient-centered outcome	Lack of consensus Subjective Complex questionnaires No clinically relevant difference defined for power calculations and non-inferiority not feasible

Timsit JF et al. Intensive Care Med 2017

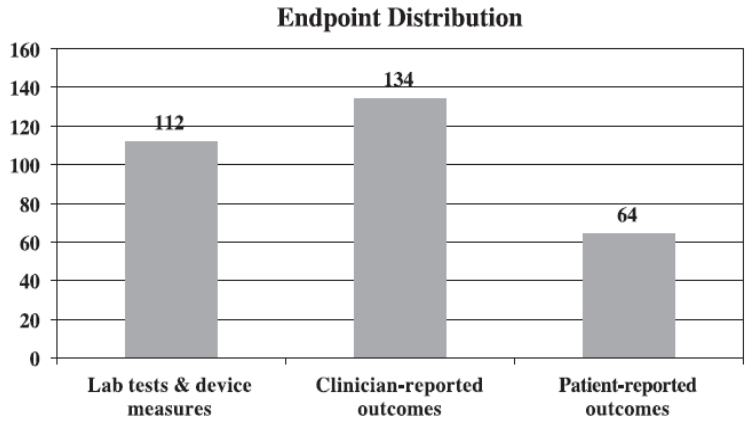
Endpoint	Advantages	Disadvantages
Clinical cure (resolution of symptoms) [23]	Sensitive (especially if mortality rates are low)	No consensual definition: what symptoms should be included? Symptoms may be related to other diseases Possible subjectivity of assessment Different time-points for assessment may be necessary for each symptom
Microbiological cure Emergence of resistance [25, 26]	Objective Simple definition	Not relevant for all pathogens Requires isolation of a causative pathogen at baseline Requires multiple and sometimes invasive microbiological samples Requires homogenous and reproducible laboratory methods Does not correlate with clinical cure in some diseases (e.g., VAP)
Biomarkers [27]	Can be measured early in treatment before changes in treatment confound the effect Large differences could be detected resulting in smaller sample size	Requires a previous demonstration of surrogate properties No definition of a clinically meaningful difference for power calculations

Timsit JF et al. Intensive Care Med 2017

Endpoint	Advantages	Disadvantages
Antibiotic-free survival [44]	Improved power	Possible impact for the community difficult to ascertain and not directly related to individual impact May equally score patients dying at day 1 and patients alive and still under antimicrobiasl at end of study Difficult to define—concomitant antibiotics may be given to ensure coverage of all pathogens
Composite endpoint [30]	Improved power Can assess benefits and harms simultaneously	Difficult to interpret if there is collinearity between endpoints Clinically relevant effects could be diluted or even hidden by less important components
Hierarchical endpoint [35, 36]	Potential for providing an unified scale Potentially improves the power to detect superiority	Complexity of assigning a rank—previous databases need to explore how different it is to current endpoints Requires a previous consensual definition of the clinically meaningful difference

Timsit JF et al. Intensive Care Med 2017

- Laboratory test/device measurements endpoints
- Clinician reported outcomes (CROs)= κλινική βελτίωση και κλινική ίαση
- Patient reported outcomes (PROs)- Health related quality of life (HRQL)
- Effectiveness endpoints – PRO endpoints

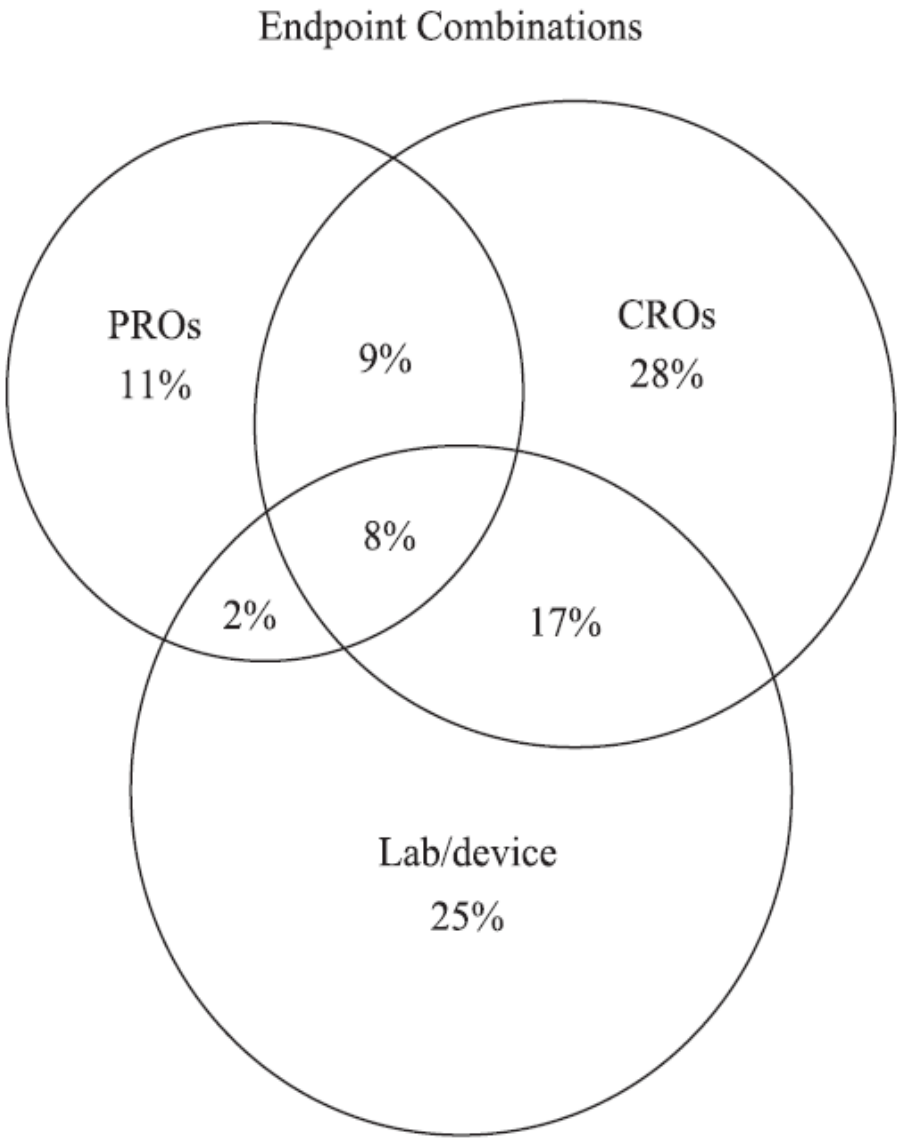


Willke R et al. Controlled Clinical Trials 2004; 535-552

PROs (patient reported outcomes)

"patient-reported outcomes" was proposed as an umbrella term to describe a broad spectrum of disease and treatment outcomes reported subjectively by the patient

- Άμεσα δεδομένα από το θεραπευτικό όφελος (πώς αισθάνονται και πώς λειτουργούν)
- Εμπειρία από τη λαμβανόμενη θεραπεία
- Βελτίωση της σχέσης ιατρού-ασθενή
- Βελτίωση της συμμόρφωσης με την αγωγή



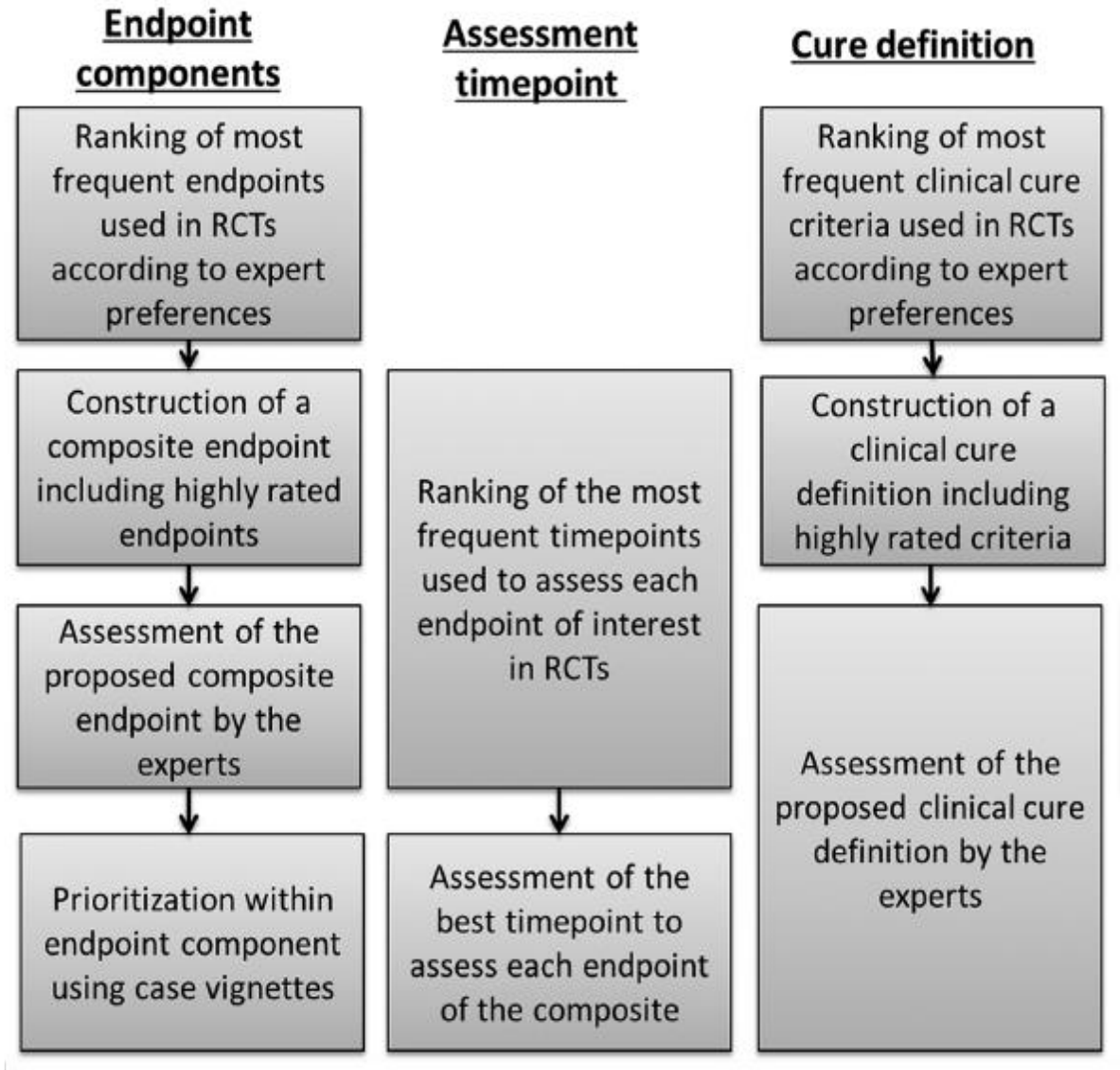
CROs requiring patient input are distinguished from clinician administered PROs in that the former requires clinician judgment or interpretation when recording answers, while the latter involves recording precise, unmodified patient responses to prespecified questions

Willke R et al. Controlled Clinical Trials 2004; 535-552

Early clinical response vs late clinical response

Baseline patient characteristics

Mortality rate



Rank	Item
1	Clinical cure
2	ACM
3	MV-free days
4	Improvement in oxygenation parameters
5	No. of days before resolution
6	CPIS [9] decrease
7	Microbiological cure
8	Safety
9	PCT decrease
10	Acquisition of antimicrobial resistance

Abbreviations: ACM, all-cause mortality; CPIS, Clinical Pulmonary Infection Score; MV, mechanical ventilation; PCT, procalcitonin; SD, standard deviation.

Table 2. Summary of Phase 3 Trials in Patients With cUTI; Micro-ITT Populations

Study	Day of Evaluation	Microbio-logical Success*	Clinical Response	Microbiological Success + Clinical Response	Source
1	7-10 d post-Rx	171/208 (82.2%)	188/208 (90.4%)	164/208 (78.8%)	Trial datasets
2	7-10 d post-Rx	149/192 (77.6%)	166/192 (86.5%)	139/192 (72.4%)	Trial datasets
3	5-9 d post-Rx	197/227 (86.8%)	185/227 (81.5%)	180/227 (79.3%)	Trial datasets
	5-9 d post-Rx	209/248 (84.3%)	206/248 (83.1%)	197/248 (79.4%)	Trial datasets
4	5-9 d post-Rx	106/139 (76.3%)	112/139 (80.6%)	104/139 (74.8%)	Trial datasets
	5-9 d post-Rx	54/73 (74.0%)	55/73 (75.3%)	51/73 (69.9%)	Trial datasets
5	6-9 d post-Rx	257/325 (79.1%)	291/325 (90.0%)	241/325 (74.2%)	Trial datasets
	6-9 d post-Rx	253/323 (78.3%)	260/323 (80.5%)	233/323 (72.1%)	Trial datasets
6	6-9 d post-Rx	278/337 (82.5%)	294/337 (87.2%)	255/337 (75.7%)	Trial datasets
7	3-9 d post-Rx	240/317 (75.7%)	224/317 (70.7%)	201/317 (63.4%)	Trial datasets
	3-9 d post-Rx	229/302 (75.8%)	205/302 (67.9%)	193/302 (63.9%)	Trial datasets

Table 3. Summary of Phase 3 Trials Evaluating Responses at End of IV Therapy

Study Group	Mean Duration of IV Therapy	Microbiological Success During Treatment With IV*	Clinical Response at End of IV Therapy#	Microbiological Success + Clinical Response	Source
1	4.0 days	100%	106/216 (49.1%)	106/216 (49.1%)	Trial datasets
2	4.1 days	100%	113/230 (49.1%)	113/230 (49.1%)	Trial datasets
3	4.0 days	100%	87/130 (66.9%)	87/130 (66.9%)	Trial datasets
4	4.0 days	100%	47/67 (70.1%)	47/67 (70.1%)	Trial datasets
5	5.4 days	100%	230/317 (72.5%)	230/317 (72.5%)	Trial datasets
6	5.3 days	100%	224/311 (72.0%)	224/311 (72.0%)	Trial datasets
7	5.5 days	100%	230/329 (69.9%)	230/329 (69.9%)	Trial datasets
DerSimonian and Laird random effects meta-analysis for the microbiological success + clinical response: 64% (95% CI: 56%, 72%) (See notes 8 and 9 at the bottom of Table 1.)					

* Criteria for microbiological success was evaluated using fewer than 10^4 CFU/mL.

The five symptoms that were evaluated as having complete resolution in this analysis were symptoms evaluated among all seven study groups: dysuria, frequency, suprapubic pain, urgency, and flank pain.

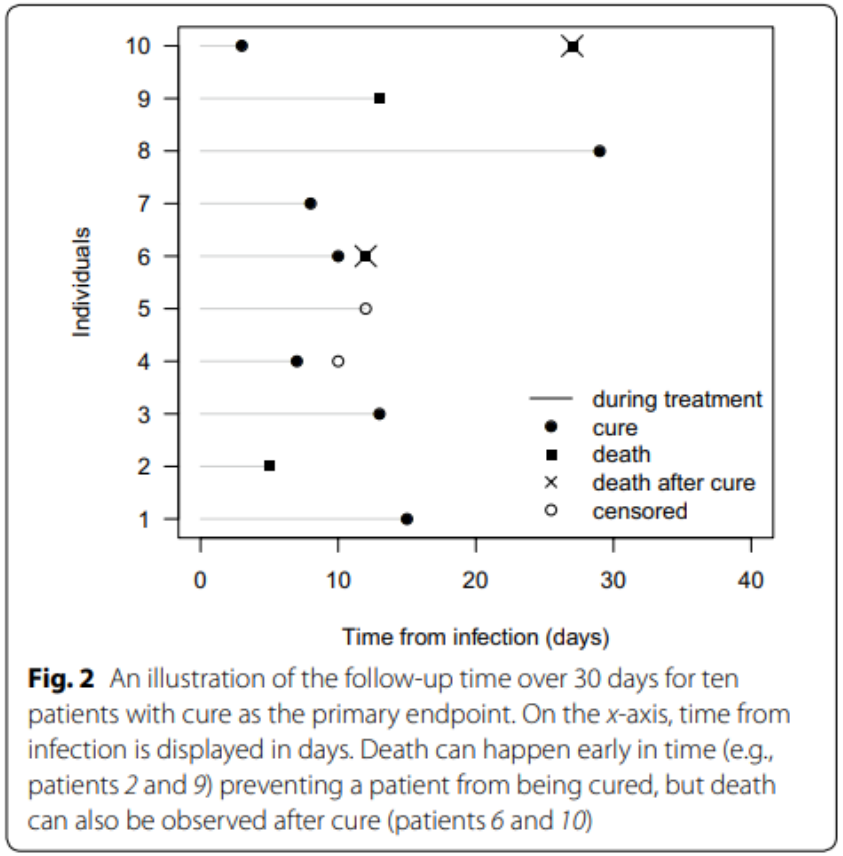


Fig. 2 An illustration of the follow-up time over 30 days for ten patients with cure as the primary endpoint. On the *x*-axis, time from infection is displayed in days. Death can happen early in time (e.g., patients *2* and *9*) preventing a patient from being cured, but death can also be observed after cure (patients *6* and *10*)

A hierarchical nested design is proposed by Huque et al. in order to overcome the problems associated with RCTs specifcally focused on treatment of infections caused by MDROs

Secondary safety endpoints that could capture this wider context at an individual level include endogenous resistance development, impact on the microbiome, i.e. colonization with MDROs after treatment, incidence of Clostridium difficile infections or super-infections.

BMJ Open

Clinical effectiveness and bacteriological eradication of three different Short-COurse antibiotic regimens and single-dose fosfomycin for uncomplicated lower Urinary Tract infections in adult women (SCOUT study): study protocol for a randomised clinical trial

Methods and analysis This will be a pragmatic, multicentre, parallel group, open trial. Women aged 18 or older and with symptoms of uLUTI and a positive urine dipstick analysis will be randomised to one of the following four groups: a single dose of 3 g of fosfomycin, 2 days of 3 g of fosfomycin o.d., 3 days of pivmecillinam 400 mg three times per day (t.i.d) or 5 days of nitrofurantoin 100 mg t.i.d. A total sample of 1120 patients was calculated. The primary endpoint is clinical effectiveness at day 7, defined as cure of symptoms reported by the patients in a diary including four symptoms: dysuria, urgency, frequency and suprapubic pain, which will be scored on a 4-point severity scale (not present/mild/moderate/severe). Follow-up visits are scheduled at days 7 (phone call), 14 and 28 for assessing evolution. Urine samples will be collected in the three on-site visits and urine cultures performed. If positive, antibiograms for the three antibiotics studied will be performed. Bacterial eradication will be measured at days 14 and 28.

Πολυκεντρική
Γυναίκες >18 ετών
Συμπτώματα uLUTI
Θετικό dipstick ούρων

Τυχαιοποίηση σε 4 ομάδες:

1. Fosfomycin 3gr άπαξ
2. Fosfomycin 3gr για 2 συνεχόμενες ημέρες
3. Pivmecillinam 400mg tid για 3 ημέρες
4. Nitrofurantoin 100mg tid για 5 ημέρες

Primary endpoint
Clinical effectiveness at day 7=ύφεση των συμπτωμάτων όπως αναφέρονται από τους ασθενείς σε ημερολόγιο αναφερόμενοι σε 4 συμπτώματα (δυσουρία, έπειξη προς ούρηση, συχνουρία και υπερηβικό άλγος)
Κλίμακα 4-point

FUP: 7 (phone call), 14 και 28
Εξέταση ούρων στις 3 επισκέψεις
Βακτηριακή εκρίζωση στις 14 και 28 ημέρες

Therapeutic Advances in Infectious Disease Original Research

Structured patient interview to assess clinical outcomes in complicated urinary tract infections in the APEKS-cUTI study: pilot investigation

Ther Adv Infectious Dis
2021, Vol. 8: 1–10
DOI: 10.1177/20499361211058257

Simon Portsmouth, Roger Echols, Kiichiro Toyoizumi, Glenn Tillotson and Tsutae Den Nagata

Η APEKS-cUTI ήταν μια τυχαιοποιημένη μελέτη 2:1, πολυκεντρική, φάσης II, διπλά τυφλή, non-inferiority που συνέκρινε την imipenem-cilastatin με την cefiderocol για την θεραπεία των cUTI που προκαλούνται από gram-αρνητικά παθογόνα σε ενήλικες με παράγοντες κινδύνου για MDR λοιμώξεις.

Το πρωτογενές καταληκτικό σημείο ήταν να συγκριθεί η κλινική ανταπόκριση και η μικροβιακή εκρίζωση στη στιγμή test of cure (TOC) μεταξύ των 2 θεραπευτικών επιλογών

Structured-patient interview clinical cure rates ήταν 89.7% για την cefiderocol και 84.9% για την Imipenem-cilastatin

Table 1. Structured patient interview used to evaluate patient-reported symptoms.

Symptoms:	Is the symptom present?	If yes, enter severity
Feeling feverish	□YES □NO	□MILD □MODERATE □SEVERE
Shaking/chills	□YES □NO	□MILD □MODERATE □SEVERE
Malaise	□YES □NO	□MILD □MODERATE □SEVERE
Frequency of urination	□YES □NO	□MILD □MODERATE □SEVERE
Urgency of urination	□YES □NO	□MILD □MODERATE □SEVERE
Dysuria (painful urination)	□YES □NO	□MILD □MODERATE □SEVERE
Urinary incontinence	□YES □NO	□MILD □MODERATE □SEVERE
Cloudy or change in color of urine	□YES □NO	□MILD □MODERATE □SEVERE
Nausea	□YES □NO	□MILD □MODERATE □SEVERE
Vomiting	□YES □NO	□MILD □MODERATE □SEVERE
Pain above the pubic bone	□YES □NO	□MILD □MODERATE □SEVERE
Abdominal pain	□YES □NO	□MILD □MODERATE □SEVERE
Flank/back/costovertebral angle pain or tenderness	□YES □NO	□MILD □MODERATE □SEVERE
Back pain	□YES □NO	□MILD □MODERATE □SEVERE
Other[a] specify:_____	□YES □NO	□MILD □MODERATE □SEVERE

- Day-2 έως Day 1
- Early assessment (EA)
- End of treatment (EOT)
- Test of Cure (TOC)
- Follow up (FUP)

- Υποχώρηση συμπτωμάτων
- Βελτίωση συμπτωμάτων
- Απουσία νέου συμπτώματος

Table 2. Interviewer reporting of post-baseline patient-reported symptoms.

Symptoms		**Severity**
Symptoms:	**Symptoms findings (since the last visit)**	**If finding was 2–5, then enter severity[a]**
For each of the 14 pre-specified symptoms: Feeling feverish Shaking/chills Malaise Frequency of urination Urgency of urination Dysuria (painful urination) Urinary incontinence Cloudy or change in color of urine Nausea Vomiting Pain above the pubic bone Abdominal pain Flank/back/ costovertebral angle pain or tenderness Back pain Other[b]	☐ **0 – Not present at last assessment** ☐ 1 – Resolved or returned to the state before the UTI ☐ 2 – Not present at baseline/last assessment but new onset ☐ 3 – Continuing and increased since the last assessment ☐ 4 – Continuing but decreased since the last assessment ☐ 5 – Continuing and no change since the last assessment	☐ **MILD** ☐ MODERATE ☐ SEVERE

Table 3. Definitions of investigator-associated clinical and microbiological responses.

Definitions	
Clinical response	Assessed by the investigator as resolution or improvement in core clinical signs and symptoms of cUTI present at baseline and no new symptom emerged, or return to pre-infection baseline.
Clinical failure	No apparent response to therapy, persistence of signs and/or symptoms of cUTI infection, or reappearance of signs and/or symptoms that were present at an earlier visit.
Indeterminate clinical response	Observed when the clinical response could not be determined due to the patient being lost to follow-up.
Microbiological eradication	Eradication of baseline Gram-negative pathogen by quantitative microbiological assessment (i.e., urine culture of the causative pathogen growing at $\geqslant 10^5$ CFU/mL at baseline was reduced to $<10^4$ CFU/mL).
Microbiological failure	Persistence of baseline Gram-negative pathogen by quantitative microbiological assessment (i.e., urine culture of the causative pathogen growing at $\geqslant 10^5$ CFU/mL at baseline grew at $\geqslant 10^4$ CFU/mL).
Indeterminate microbiological response	No urine culture was taken or a urine culture that could not be interpreted for any reason.