ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ

ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ

ΙΑΤΡΙΚΗ ΣΧΟΛΗ

ΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ «ΑΤΤΙΚΟΝ»

Δ'ΠΑΝΕΠΙΣΤΗΜΙΑΚΗ ΠΑΘΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ

ΔΙΕΥΘΥΝΤΗΣ: Καθηγητής Δημήτριος Τ. Μπούμπας

ΣΥΝΝΟΣΗΡΟΤΗΤΕΣ ΚΑΙ ΔΕΙΚΤΕΣ ΠΟΙΟΤΙΚΗΣ ΦΡΟΝΤΙΔΑΣ ΣΤΟΝ ΣΥΣΤΗΜΑΤΙΚΟ ΕΡΥΘΗΜΑΤΩΔΗ ΛΥΚΟ (ΣΕΛ): ΣΥΓΧΡΟΝΙΚΗ ΚΑΙ ΠΡΟΟΠΤΙΚΗ ΜΕΛΕΤΗ

ΔΙΔΑΚΤΟΡΙΚΗ ΔΙΑΤΡΙΒΗ

ΑΘΗΝΑ 2023

ΑΙΚΑΤΕΡΙΝΑ ΧΑΒΑΤΖΑ

NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS

SCHOOL OF HEALTH SCIENCES

SCHOOL OF MEDICINE

«ATTIKON» UNIVERSITY HOSPITAL

4TH DEPARTMENT OF INTERNAL MEDICINE

COMMORBIDITIES AND QUALITY INDICATORS IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

DOCTORAL THESIS

ATHENS 2023

AIKATERINA CHAVATZA

ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ

ΙΑΤΡΙΚΗ ΣΧΟΛΗ

Δ'ΠΑΝΕΠΙΣΤΗΜΙΑΚΗ ΠΑΘΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ

ΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΑΤΤΙΚΟΝ

ΔΙΕΥΘΥΝΤΗΣ: Καθηγητής Δημήτριος Τ. Μπούμπας

Υποψήφια Διδάκτωρ: Αικατερίνα Χαβάτζα

Επιβλέπον μέλος ΔΕΠ: Καθηγητής Δημήτριος Μπούμπας

Τόπος εκπόνησης διδακτορικής διατριβής: Δ' Πανεπιστημιακή Παθολογική Κλινική, Πανεπιστημιακό Γενικό νοσοκομείο «ΑΤΤΙΚΟΝ»

Γνωστικό αντικείμενο: « Συννοσηρότητες και δείκτες ποιοτικής φροντίδας στον Συστηματικό Ερυθηματώδη Λύκο (ΣΕΛ): Συγχρονική και προοπτική μελέτη»

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1. **Δημήτριος Μπούμπας:** Καθηγητής Παθολογίας- Ρευματολογίας
2. **Δημήτριος Βασιλόπουλος:** Καθηγητής Παθολογίας-Ρευματολογίας
3. **Σωτήριος Τσιόδρας:** Καθηγητής Παθολογίας-Λοιμώξεων

ΓΕΝΙΚΑ ΣΤΟΙΧΕΙΑ ΔΙΔΑΚΤΟΡΙΚΗΣ ΔΙΑΤΡΙΒΗΣ

Α) Ημερομηνία αιτήσεως υποψηφίου: 8/3/2019

Β) Ημερομηνία ορισμού τριμελούς επιτροπής: 12/4/2019

Γ) Μέλη εφταμελούς συμβουλευτικής επιτροπής:

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5. **Χαράλαμπος Παπαγόρας:** Καθηγητής Ρευματολογίας
6. **Πρόδρομος Σιδηρόπουλος:** Καθηγητής Ρευματολογίας
7. **Γεώργιος Μπερτσιάς:** Καθηγητής Ρευματολογίας

Δ) Ημερομηνία έγκρισης του θέματος: 12/6/2019

Ε) Ημερομηνία κατάθεσης διδακτορικής διατριβής:6/9/2023

ΣΤ) Ημερομηνία παρουσίασης διδακτορικής διατριβής: 27/10/2023

Ζ) Βαθμός διδακτορικής διατριβής: «ΑΡΙΣΤΑ»

Στην αδερφή μου Αλεξάνδρα,
που η βαθιά της αφιέρωση φωτίζει τον δρόμο μου

Στην οικογένειά μου,
για την αγάπη και τη στήριξη

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Σε αυτούς,
που μυστικά στηρίζουν και εμπνέουν την καρδιά μου

ΠΕΡΙΕΧΟΜΕΝΑ

ΠΙΝΑΚΑΣ ΣΥΝΤΟΜΕΥΣΕΩΝ

ΣΥΝΤΟΜΕΥΣΕΙΣ	ΕΞΗΓΗΣΗ
ACR	American college of rheumatology
AHQR	Agency for healthcare research and quality
AIDS	Acquired immunodeficiency syndrome
ANAs	Antinuclear antibodies
Anti-ds-DNA	Double stranded DNA antibodies
BAFF	B-cell activating factor
BILAG	British Isles lupus activity group
BLyS	B-lymphocyte stimulator
CD40L	Cluster of differentiation 40 ligand
CMV	Cytomegalovirus
CNS	Central nervous system
DAMPs	Damage-associated molecular patterns
DMARDs	Disease modifying antirheumatic drugs
EBV	Epstein Barr virus
ESRD	End-stage renal disease
EULAR	European league against rheumatism
EXPH	European Commission's Expert Panel on Effective Ways of Investing In Health
GWAS	Genome-wide association studies
HERVs	Human endogenous retroviruses
HIV	Human immunodeficiency virus
IFN	Interferon
IL	Interleukin
IOM	Institute of medicine
LLDAS	Lupus low disease activity state
MHC	Major histocompatibility complex
NCQA	National Committee on Quality Assurance
NETs	Neutrophil extracellular traps

NICE	National Institute for Health and Care Excellence
NPSLE	Neuropsychiatric systemic lupus erythematosus
NQF	National Quality Foundation
PAMPs	Pathogen-associated molecular patterns
PCBs	Polychlorinated biphenyls
PGA	Physician global assessment
QIs	Quality indicators
SDI	SLICC/ACR Damage Index
SELENA-SLEDAI	Safety of estrogens in lupus erythematosus national assessment
SLE	Systematic lupus erythematosus
SLEDAI	Systemic lupus erythematosus disease activity index
SLICC	Systemic lupus international collaborating clinics
SLR	Systematic literature review
TLRs	Toll- like receptors
TNF	Tumor necrosis factor
UV	Ultraviolet
WHO	World Health Organization

ΒΙΟΓΡΑΦΙΚΟ ΣΗΜΕΙΩΜΑ

ΠΡΟΣΩΠΙΚΑ ΣΤΟΙΧΕΙΑ

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ΠΡΟΠΤΥΧΙΑΚΗ- ΠΤΥΧΙΑΚΗ ΕΚΠΑΙΔΕΥΣΗ

2011-2017: Ιατρική Σχολή, Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών
2008-2011: Α΄Αρσάκειο Γενικό Λύκειο Ψυχικού, Αθήνα

ΜΕΤΑΠΤΥΧΙΑΚΕΣ ΣΠΟΥΔΕΣ-ΕΚΠΑΙΔΕΥΣΗ

09/2021- σήμερα: **Διατμηματικό ΠΜΣ Βιοστατιστικής και Επιστήμης Δεδομένων Υγείας**, Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών, Ιατρική Σχολή- Τμήμα Μαθηματικών

03/2021-02/2023: Ειδικευόμενη Παθολογίας, Δ' Πανεπιστημιακή Παθολογική Κλινική, Πανεπιστημιακό Γενικό Νοσοκομείο ΑΤΤΙΚΟΝ

06/2019- σήμερα: **Εκπόνηση Διδακτορικής Διατριβής με θέμα: «Δείκτες Ποιοτικής Φροντίδας στον Συστηματικό Ερυθηματώδη Λύκο»,** Ιατρική Σχολή, Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών

ΣΕΜΙΝΑΡΙΑ-ΔΙΠΛΩΜΑΤΑ

02/2018: Σεμινάριο Εξειδικευμένης Υποστήριξης της Ζωής (ALS)
11/2017: Σεμινάριο Βασικής Υποστήριξης της Ζωής (BLS)
6/2017: Advanced Trauma Life Support (ATLS)
5/2017: Τριήμερο Εκπαιδευτικό Σεμινάριο στις Λοιμώξεις
5/2017: 6th Student Emergency Abdominal Surgery Course

ΥΠΟΤΡΟΦΙΕΣ

06/2019-03/2021: Υποτροφία για την εκπόνηση διδακτορικής διατριβής στα πλαίσια του προγράμματος «*LUPUSCARE: Precision care in Systemic autoimmunity: an integrated multi-tissue/level approach for Systemic Lupus Erythematosus»,* Ίδρυμα Ιατροβιολογικών Ερευνών Ακαδημίας Αθηνών (ΙΙΒΕΑΑ)

ΕΠΑΓΓΕΛΜΑΤΙΚΗ ΕΜΠΕΙΡΙΑ

03/2021-02/2023: Ειδικευόμενη Παθολογίας, Δ' Πανεπιστημιακή Παθολογική Κλινική, Πανεπιστημιακό Γενικό Νοσοκομείο ΑΤΤΙΚΟΝ

06/2019-03/2021: Δ' Παθολογική Κλινική ΠΓΝ ΑΤΤΙΚΟΝ, Ρευματολογικό Ιατρείο. **Πανεπιστημιακός υπότροφος** στα πλαίσια υλοποίησης του προγράμματος **«*LUPUSCARE**: Precision care in Systemic*

autoimmunity: an integrated multi-tissue/level approach for Systemic LUPUS Erythematosus (SLE)»

02/2018- 04/2019: **Ιατρός Υπηρεσίας Υπαίθρου**, Περιφερικό Ιατρείο Συκιάς Χαλκιδικής, 4η ΥΠΕ Μακεδονίας Θράκης

09/2017- 01/2018: Δ' Παθολογική Κλινική ΠΓΝ ΑΤΤΙΚΟΝ. **Καθήκοντα πρωτοετούς ειδικευομένου.** Άμισθη Εργασία

09/2015- 03/2016: Ιατρείο Καρδιακής Ανεπάρκειας, Γ.Ν. Αλεξάνδρα. **Πρακτική Άσκηση**

10/2014-07/2016: Ρευματολογικό Ιατρείο ΠΓΝ ΑΤΤΙΚΟΝ. **Πρακτική Άσκηση**

ΕΡΓΑΣΤΗΡΙΑΚΗ ΕΜΠΕΙΡΙΑ

11/2015- 12/2016: Ίδρυμα Ιατροβιολογικών Ερευνών Ακαδημίας Αθηνών (ΙΙΒΕΑΑ), Καθηγητής Δημήτριος Μπούμπας

ΕΠΑΓΓΕΛΜΑΤΙΚΕΣ ΑΔΕΙΕΣ

2017: Άδεια άσκησης Ιατρικής

ΙΑΤΡΙΚΕΣ ΕΤΑΙΡΙΕΣ

2019- σήμερα: Ιατρικός Σύλλογος Αθηνών
2018- 2019: Ιατρικός Σύλλογος Χαλκιδικής

ΔΙΔΑΚΤΙΚΗ ΕΜΠΕΙΡΙΑ

2019- σήμερα:
-Βιβλιογραφική ενημέρωση, παρουσίαση περιπτώσεων ασθενών και ερευνητικής δραστηριότητας στις **Εκπαιδευτικές Συναντήσεις της Μονάδας Ρευματολογίας**, Δ' Πανεπιστημιακή Παθολογική Κλινική, ΠΓΝ ΑΤΤΙΚΟΝ
-Βιβλιογραφική ενημέρωση και παρουσίαση περιπτώσεων ασθενών στις **Εκπαιδευτικές Συναντήσεις στα πλαίσια ειδικότητας της Παθολογίας,** Δ' Πανεπιστημιακή Παθολογική Κλινική, ΠΓΝ ΑΤΤΙΚΟΝ
-Παρουσίαση στις **Λοιμωξιολογικές Συναντήσεις** της Δ' Πανεπιστημιακής Παθολογικής Κλινικής, ΠΓΝ ΑΤΤΙΚΟΝ (Συντονιστής: Κ. Θωμάς)
-Εκπαίδευση φοιτητών Ιατρικής 6ου έτους στα πλαίσια του τριμήνου Παθολογίας, Δ' Πανεπιστημιακή Παθολογική Κλινική, ΠΓΝ ΑΤΤΙΚΟΝ

ΔΗΜΟΣΙΕΥΣΕΙΣ

1. **Katerina Chavatza**, Myrto Kostopoulou, Dionysis Nikolopoulos, Ourania Gioti, Konstantina Togia, Laura Andreoli, Martin Aringer, John Boletis, Andrea Doria, Frederic A Houssiau, David

Jayne, Marta Mosca, Elisabet Svenungsson, Angela Tincani, George Bertsias, Antonis Fanouriakis, Dimitrios T Boumpas. Annals of the Rheumatic Diseases, Quality indicators for systemic lupus erythematosus based on the 2019 EULAR recommendations: development and initial validation in a cohort of 220 patients

2. Ourania Gioti , **Katerina Chavatza** , Myrto Nikoloudaki ,Spyridon Katechis , George Bertsias , Dimitrios T Boumpas, Antonis Fanouriakis. Lupus, Residual disease activity and treatment intensification in systemic lupus erythematosus: A cross-sectional study to quantify the need for new therapies

3. N.N. Kapsala, D.S. Nikolopoulos, S.P. Flouda, **A.P. Chavatza**, D.D. Tseronis, M.D. Aggelakos, P.P. Katsimbri, G.K. Bertsias, A.C. Fanouriakis, D.T. Boumpas. Clinical and Experimental Rheumatology, From first symptoms to diagnosis of systemic lupus erythematosus: mapping the journey of patients in an observational study

4. D Nikolopoulos, M Kostopoulou, A Pieta, T Karageorgas, D Tseronis, **K Chavatza**, S Flouda, P Rapsomaniki, A Banos, E Kremasmenou, V Tzavara, P Katsimbri, A Fanouriakis, and DT Boumpas. Lupus, Evolving phenotype of systemic lupus erythematosus in Caucasians: low incidence of lupus nephritis, high burden of neuropsychiatric disease and increased rates of late-onset lupus in the 'Attikon' cohort

5. Dionysis S Nikolopoulos, Myrto Kostopoulou, Antigoni Pieta, Sofia Flouda, **Katerina Chavatza**, Aggelos Banos, John Boletis, Pelagia Katsimbri, Dimitrios T Boumpas, Antonis Fanouriakis. Lupus Science & Medicine, Transition to severe phenotype in systemic lupus erythematosus initially presenting with non-severe disease: implications for the management of early disease

6. Maria Karampeli, Konstantinos Thomas, Sofia Flouda, **Aikaterina Chavatza**, Dionisios Nikolopoulos, Antigone Pieta, Dimitrios Tseronis, Michail Aggelakos, Dimitra Kassara, Vasiliki Tzavara, Pelagia Katsimbri, Dimitrios Boumpas, Theofanis Karageorgas. Mediterranenan Journal of Rheumatology, Interstitial Pneumonia with Autoimmune Features (IPAF): A Single-Centre, Prospective Study

ΠΑΡΟΥΣΙΑΣΕΙΣ ΣΕ ΔΙΕΘΝΗ ΣΥΝΕΔΡΙΑ

1.Katerina Chavatza, Myrto Kostopoulou, Dionysis Nikolopoulos, Ourania Gioti, Konstantina Togia, Sofia Flouda, Noemin Kapsala, Maria Kosmetatou, Georgia-Savina Moysidou, Alexandros Grivas, Antigone Pieta, Aliki Ntourou, Panagiota Rapsomaniki, Thaleia Gerogianni, Dimitrios Tseronis, Michail Aggelakos, Theofanis Karageorgas, Pelagia Katsimpri, Laura Andreoli, Martin Aringer, John N. Boletis, Andrea Doria, Frederic Houssiau, David Jayne, Marta Mosca, Elisabet Svenungsson, Angela Tincani, George Bertsias, Antonis Fanouriakis, Dimitrios Boumpas. EULAR Recommendation-based Quality Indicators (QIs) for Systemic Lupus Erythematosus (SLE): Elaboration, Final Set, Performance and Initial Validation, Annual EULAR Congress 2021

2.Ourania Gioti, **Katerina Chavatza**, Georgios Belevonis, Sofia Koutsoviti, Chaido Katsimpari, Ioannis Sofianos, Athanasia Tatsi, Prokopis Tzanis, Argyro Lazarini, Kalliopi Klavdianou, Iro Ioanna Giannakopoulou, Eleni Kalavri, Evangelos Theotikos, Antonia Elezoglou, Dimitrios Boumpas, Antonis Fanouriakis. Unmet treatment needs in Systemic Lupus Erythematosus (SLE): A cross-sectional assessment of disease activity in SLE patients during the last visit, Annual EULAR Congress 2021

3.Alexandros Grivas, Irene Kapniari, **Katerina Chavatza**, Sofia Flouda, Noemin Kapsala, Dimitrios Tseronis, Michail Aggelakos, Theofanis Karageorgas, Evagelia Papadavid, Dimitrios Boumpas, Pelagia Katsimpri. The "ATTIKON" psoriatic arthritis (PSA) joint rheumatology-dermatology cohort: Evidence for severe polyarthritic phenotype and increased burden of comorbidities, Annual EULAR Congress 2021

4.Noemin Kapsala, Sofia Flouda, Dionysis Nikolopoulos, **Katerina Chavatza**, Antigone Pieta, Alexandros Grivas, Aliki Ntourou, Konstantina Togia, Panagiota Rapsomaniki, Thaleia Gerogianni, Dimitrios Tseronis, Michail Aggelakos, Theofanis Karageorgas, Pelagia Katsimpri, George Bertsias, Antonis Fanouriakis, Dimitrios Boumpas. The Journey of Patients from First Symptoms to Diagnosis of Systemic Lupus Erythematosus (SLE): An Observational Study, Annual EULAR Congress 2021

5.**Katerina Havatza**, Konstantina Togia, Sofia Flouda, Antigoni Pieta, Ourania Gioti, Dionysis Nikolopoulos, Noemin Kapsala, Aliki Ntourou, Panagiota Rapsomaniki, Thaleia Gerogianni, Dimitrios Tseronis, Michail Aggelakos, Theofanis Karageorgas, Pelagia Katsimpri, George Bertsias, Konstantinos Thomaσ, Dimitrios Boumpas, Antonis Fanouriakis. Therapeutic Targets and Quality Indicators in Systemic Lupus Erythematosus (SLE), defined according to the 2019 update of the EULAR recommendations: Data from the "Attikon" lupus cohort, Annual EULAR Congress 2020

6.Maria Karampeli, Konstantinos Thomas, Dimitrios Tseronis, Michail Aggelakos, Dimitra Kassara, **Katerina Havatza**, Sofia Flouda, Dionysis Nikolopoulos, Antigoni Pieta, Vasiliki Tzavara, Pelagia Katsimbri, Dimitrios Boumpas, Theofanis Karageorgas Interstitial pneumonia with autoimmune features (IPAF): A single center, prospective study, Annual EULAR Congress 2020

ΠΑΡΟΥΣΙΑΣΕΙΣ ΣΕ ΕΛΛΗΝΙΚΑ ΣΥΝΕΔΡΙΑ

1.**Α.Χαβάτζα**, Κ.Τόγια, Σ.Φλούδα, Α.Πιέτα, Δ.Νικολόπουλος, Ο.Γιώτη, Α.Ντούρου, Θ.Γερογιάννη, Π.Κατσιμπρή, Μ.Αγγελάκος, Δ.Τσερώνης, Θ.Καράγεωργας, Κ.Θωμάς, Α.Φανουριάκης. Στόχοι θεραπείας και δείκτες ποιοτικής φροντίδας στον Συστηματικό Ερυθηματώδη Λύκο (ΣΕΛ), Πανελλήνιο Ιατρικό Συνέδριο 2020

2.Κ. Τόγια, **Α. Χαβάτζα**, Σ.Φλούδα, Ν. Καψάλα, Δ.Νικολόπουλος, Ο.Γιώτη, Α.Ντούρου, Θ.Γερογιάννη, Π. Ραψομανίκη Π.Κατσιμπρή, Μ.Αγγελάκος, Δ.Τσερώνης, Θ.Καράγεωργας,Κ.Θωμάς, Α.Φανουριάκης, Δ. Μπούμπας. Η συμμόρφωση στην θεραπευτική αγωγή σε ασθενείς με Συστηματικό Ερυθηματώδη Λύκο, Πανελλήνιο Συνέδριο Ρευματολογίας 2020

3.Γερογιάννη Θ., **Χαβάτζα Κ**., Τόγια Κ., Νικολόπουλος Δ., Γιώτη Ο., Ραψομανίκη Π., Ντούρου Α., Φλούδα Σ., Καψάλα Ν., Τσερώνης Δ., Αγγελάκος Μ., Καράγεωργας Θ., Κατσιμπρή Π., Φανουριάκης Α. Μωυσίδου, Γ., Κοσμετάτου, Μ., Μπούμπας Δ. Υποκειμενική εκτίμηση των ασθενών με Συστηματικό Ερυθηματώδη Λύκο (ΣΕΛ) για το νόσημά τους (PROs) και συσχέτιση με τον καταστροφικό πόνο, Πανελλήνιο Συνέδριο Ρευματολογίας 2020

4.Γιώτη Ο., **Χαβάτζα Α**., Μπελεβώνης Γ., Κουτσοβίτη Σ., Κατσίμπαρη Χ., Σοφιανός Ι., Τάτση Α., Τζάνης Π., Λαζαρίνη Α., Κλαυδιανού Κ., Γιαννακοπούλου Η., Καλαβρή Ε., Θεότικος Ε., Ελέζογλου Α., Μπούμπας Δ., Φανουριάκης Α. Θεραπευτικό κενό στον Συστηματικό Ερυθηματώδη Λύκο: Συγχρονική καταγραφή της ενεργότητας νόσου κατά την τελευταία επίσκεψη σε δύο κέντρα, Πανελλήνιο Συνέδριο Ρευματολογίας 2020

ΣΥΓΓΡΑΦΗ ΣΕ ΙΑΤΡΙΚΑ ΒΙΒΛΙΑ

1. Κεφάλαιο **«Προσυμπτωματικός έλεγχος (Screening)»**, στο **«Εγχειρίδιο παθολογικής ογκολογίας-Αρχική Συνδρομική Προσέγγιση για τον Παθολόγο»** (Χαϊδάρι 2023)

2. Κεφάλαιο **«Φυσιολογία και παθοφυσιολογία ανοσιακού συστήματος»**, στο **«Παιδιατρική Πνευμονολογία»** (Δεκέμβριος 2021)

ΠΡΟΛΟΓΟΣ-ΕΥΧΑΡΙΣΤΙΕΣ

Επανεξετάζοντας κάθε σκαλί στην κλίμακα της ιατρικής μου εκπαίδευσης, βρίσκομαι μπροστά σε ένα ευρύ σύνολο πληροφοριών και εμπειριών, οι οποίες συχνά παραμένουν ένα ξένο σώμα στον τρόπο με τον οποίο λειτουργούν στην καθημερινή πράξη.

Η συνολική διεργασία της εκπόνησης της διδακτορικής μου διατριβής συνετέλεσε ακριβώς σε μια σημαντική αλλαγή: σε μια διαφορετική προσέγγιση της γνώσης όχι ως «πληροφορία», αλλά ως «τρόπο». Δεν είναι πλέον ένα στάσιμο σύνολο πληροφοριών, αλλά η «δική μας», δυναμική γνώση, την οποία ψηλαφούμε και νιώθουμε σε κάθε της διάσταση.

Ειδικότερα, αναφερόμενη στην ποιότητα της ιατρικής φροντίδας, μπορώ να πω ότι η τελευταία αποτελεί το μονοπάτι μέσα από το οποίο η γνώση μοιράζεται με τον βέλτιστο τρόπο στους ασθενείς. Στην επίτευξη αυτού του σκοπού, πολύτιμο εργαλείο μπορούν να αποτελέσουν οι δείκτες ποιοτικής φροντίδας οι οποίοι στόχο έχουν να εκτιμούν τα κενά στην παρεχόμενη ιατρική φροντίδα, αλλά παράλληλα με πρακτικό τρόπο να υποδεικνύουν τον τρόπο βελτίωσης της τελευταίας. Σε αυτό το θέμα εστιάζει η διδακτορική μου διατριβή. Ειδικά στους ασθενείς με Συστηματικό Ερυθηματώδη Λύκο, παίρνοντας ως δεδομένο τη χρονιότητα, τις πολλαπλούς φαινοτύπους και τις πολλαπλές θεραπείες, η ποιότητα της ζωής παραμένει πάντα ένα σημαντικό ζητούμενο.

Η διδακτορική μου διατριβή δεν θα είχε ολοκληρωθεί χωρίς τη συμβολή της κ. Μυρτώς Κωστοπούλου, του κ. Αντώνη Φανουριάκη και του κ. Γεωργίου Μπερτσιά, οι οποίοι βοήθησαν στον τρόπο συλλογής και καταγραφής των δεδομένων, στην ανάλυσή τους, καθώς και στη συνολικότερη καθοδήγηση. Σημαντική ήταν η συμβολή της κ. Κωνσταντίνας Τόγια, η οποία συμμετείχε στη συλλογή δεδομένων ασθενών του ρευματολογικού ιατρείου, καθώς και στη διανομή ερωτηματολογίων.

Παράλληλα, οφείλω να αναφέρω όλους τους συνεργάτες του ρευματολογικού ιατρείου για τη στήριξη και τη βοήθεια σε κάθε επίπεδο, κατά τη διάρκεια εκπόνησης της εργασίας. Ιδιαίτερα, ευχαριστώ την συνάδελφό μου κ. Σοφία Φλούδα για τη στενή και άριστη συνεργασία.

Θα ήθελα ακόμα να αναφερθώ στους συναδέλφους που υπήρξαν ορόσημα στην μέχρι τώρα πορεία μου:

Πρώτα, στους δύο συναδέλφους που βρέθηκαν δίπλα μου στο ξεκίνημα της ιατρικής μου ζωής, τον κ. Φάνη Καράγεωργα και κ. Δημήτρη Τσερώνη. Το εκπαιδευτικό τους πνεύμα, η στάση τους απέναντι στους ασθενείς και η συνολικότερη βοήθειά τους αποτέλεσαν γόνιμο έδαφος πάνω στο οποίο καρποφόρησαν στη συνέχεια όλες οι προσπάθειες και προσδοκίες μου. Τους ευχαριστώ μέσα από την καρδιά μου.

Στη συνέχεια, στον επιμελητή μου κ. Κωνσταντίνο Θωμά. Υπήρξε κύριος ενθαρρυντικός παράγοντας στην απόφασή μου να ξεκινήσω διατριβή, ενώ παράλληλα η συμβολή του στη διαμόρφωση της έως τώρα ιατρικής μου σκέψης υπήρξε καθοριστική. Η αγάπη του να μοιράζεται τη γνώση είναι στοιχείο σπάνιο και αποτελεί πραγματική ευεργεσία για όλους όσους βρισκόμαστε δίπλα του. Τον ευχαριστώ θερμά.

Τέλος, θεωρώ τον εαυτό μου ευτυχή που συνάντησα και συνεργάστηκα με τον κ. Δημήτριο Μπούμπα. Πέρα από το αδιαμφισβήτητα σημαντικό ιατρικό του έργο, αποτελεί για εμένα παράδειγμα ακεραιότητας, βαθιάς ελευθερίας από μικροπρέπειες και προσωπικές φιλοδοξίες, διαρκούς εγρήγορσης. Μέσα από την εμπιστοσύνη στους συνεργάτες του και την ανάθεση πρωτοβουλιών, δεν τελεί στενό καθοδηγητικό ρόλο, αλλά συνεχώς ανοίγει νέους δρόμους. Η συνεργασία μου μαζί του με μαθαίνει διαρκώς την πραγματική διάσταση της επιτυχίας- ότι δηλαδή αποτελεί σκαλί και εφαλτήριο για κάτι νεότερο και καλύτερο. Τον ευχαριστώ πολύ.

ABSTRACT

Background

Quality of healthcare is defined as 'the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge' (IOM 1999). The definition applies both to healthcare practitioners and to all settings of care (hospitals, nursing homes and physicians' offices). Measurement of quality can help to identify problems caused by overuse, underuse or misuse of health resources. QIs are popular tools used to measure the degree of quality of care received by patients and are derived from guidelines, SLR or expert panel consensus, through the use of a systematic approach representing the current standard of care. In contrast to most guidelines or recommendations, QIs pertain to measurable aspects of healthcare, describing exactly what to do, when to do it and who is responsible for doing it, with respect to disease management and monitoring.

Methods

A total of 44 candidate QIs corresponding to diagnosis, monitoring and treatment, were independently rated for validity and feasibility by 12 experts and analysed by a modified Research and Development Corporation/University of California Los Angeles model. Adherence to the final set of QIs and correlation with disease outcomes (flares, hospitalisations and organ damage) was tested in a cohort of 220 SLE patients with a median monitoring of 2 years (IQR 2–4), at least 1 year of follow up and at least four visits over the last year.

Results

The panel selected a total of 18 QIs as valid and feasible. On average, SLE patients received 54% (95% CI 52.3% to 56.2%) of recommended care, with adherence ranging from 44.7% (95% CI 40.8% to 48.6%) for diagnosis-related QIs to 84.3% (95% CI 80.6%

to 87.5%) for treatment-related QIs. From subgroup analysis patients with severe disease were more likely to receive the indicated care (57.2%) compared with patients with moderate (53.9%) or mild (49.3%) disease (p=0.006). Similarly, higher adherence rates were observed in patients with short (<2 years) vs longer (≥2 years) disease duration (54.8% and 49.3% respectively, p=0.02). Sustained remission or low disease activity were achieved in 26.8% (95% CI 21.1% to 33.2%). Tapering of prednisone dose to less than 7.5 mg/day was achieved in 93.6% (95% CI 88.2% to 97.0%) while 73.5% (95% CI 66.6% to 79.6%) received the recommended hydroxychloroquine dose. Higher adherence to monitoring-related QIs was associated with reduced risk for a composite adverse outcome (flare, hospitalisation or damage accrual) during the last year of observation (OR 0.97 per 1% adherence rate, 95% CI 0.96 to 0.99).

As a spin-off this work, we also sought to determine the proportion of SLE patients with residual disease activity during their most recent visit, and whether patients with residual activity were offered therapy intensification. Our data suggest that about 40% of patients have evidence of residual disease activity and could qualify for novel treatments. Most treatment changes were triggered by active renal, joint, and skin disease, whereas the predictive value of SLEDAI-2K as a metric of disease activity was modest

Conclusion

We developed QIs for assessing and improving the care of SLE patients. Initial real-life data suggest face validity, but a variable degree of adherence and a need for further improvement. The low rates of CVD protection and reproductive health counselling are consistent with data from previous studies; rates for sunscreen protection and individual components for osteoporosis and vaccination (influenza, pneumococcal) QIs are also consistent with published data. In reference to potential causes related to better performance in certain indicators, we found that QI adherence rates were higher in patients with disease duration shorter than 2 years and in patients with severe disease. These observations may reflect the fact that physicians are more likely to adhere early

after diagnosis to ensure better disease control, and in patients who are more likely to develop irreversible organ damage, respectively. In summary, we have developed a set of EULAR recommendations based QIs for SLE patient care, following a comprehensive SLR and supported by expert opinion. These QIs may be used as a 'checklist' to be fulfilled in an outpatient setting, in order to improve SLE patient care by facilitating the implementation of the EULAR recommendations.

ΠΕΡΙΛΗΨΗ

Εισαγωγή

Η ποιότητα της ιατρικής φροντίδας ορίζεται ως «ο βαθμός στον οποίο οι υπηρεσίες υγείας για μεμονωμένα άτομα και πληθυσμούς, αυξάνουν την πιθανότητα των επιθυμητών εκβάσεων στην υγεία και είναι συμβατές με την τρέχουσα ιατρική γνώση» (Ινστιτούτο Ιατρικής 1999). Ο ορισμός αναφέρεται στους επαγγελματίες υγείας αλλά και σε όλες τις δομές υγείας (νοσοκομεία, γηροκομεία, ιατρεία). Η μέτρηση και αξιολόγηση της ποιότητας μπορεί να συμβάλει στην εντόπιση προβλημάτων που προκύπτουν από κακή διαχείριση των πόρων της υγείας. Οι δείκτες ποιοτικής φροντίδας είναι εργαλεία που χρησιμοποιούνται για τη μέτρηση της ποιότητας της παρεχόμενης φροντίδας και προέρχονται από το συνδυασμό κατευθυντήριων οδηγιών, τη συστηματική ανασκόπηση της βιβλιογραφίας και την αξιολόγηση από ομάδα ειδικών, μέσω μιας συστηματικής προσέγγισης. Σε αντίθεση με τις περισσότερες κατευθυντήριες οδηγίες και συστάσεις, οι δείκτες ποιοτικής φροντίδας κάνουν αναφορά σε τομείς της ιατρικής φροντίδας που μπορούν να ποσοτικοποιηθούν και περιγράφουν με ακρίβεια ποιος είναι υπεύθυνος, με ποιο τρόπο και πότε ακριβώς πρέπει να κάνει μια ιατρική πράξη.

Μεθοδολογία

Ένα σύνολο από 44 δείκτες ποιοτικής φροντίδας σχετιζόμενοι με τη διάγνωση, την παρακολούθηση και την θεραπεία, βαθμολογήθηκαν για την εγκυρότητα και την ευκολία εφαρμογής, από 12 ειδικούς, ενώ παράλληλα η ανάλυση βασίστηκε στη μέθοδο RAND/UCLA. Η εφαρμογή του τελικού σετ δεικτών ποιοτικής φροντίδας και η συσχέτιση με τις εκβάσεις της νόσου (εξάρσεις, νοσηλείες, βλάβη οργάνων-στόχων), ελέγχθηκε σε κοορτή 220 ασθενών με συστηματικό ερυθηματώδη λύκο, οι οποίοι είχαν μέσο χρόνο παρακολούθησης 2 έτη, έπρεπε να έχουν παρακολουθηθεί τουλάχιστον

ένα χρόνο και να έχουν τουλάχιστον τέσσερις επισκέψεις το τελευταίο έτος, ως κριτήριο ένταξης.

Αποτελέσματα

Η ομάδα ειδικών κατέληξε σε ένα σύνολο 18 δεικτών ποιοτικής φροντίδας, λαμβάνοντας υπόψη ως κριτήριο επιλογής, την εγκυρότητα και την δυνατότητα εφαρμογής. Κατά μέσο όρο, οι ασθενείς με λύκο έλαβαν 54% (95% CI 52.3% - 56.2%) της προτεινόμενης φροντίδας, με τη συμμόρφωση να κυμαίνεται από 44.7% (95% CI 40.8% - 48.6%), για δείκτες ποιοτικής φροντίδες σχετιζόμενους με τη διάγνωση, έως 84.3% (95% CI 80.6% - 87.5%) για δείκτες σχετιζόμενους με τη θεραπεία. Από την περαιτέρω ανάλυση σε υποομάδες, φάνηκε ότι ασθενείς με σοβαρή νόσο ήταν πιο πιθανό να έχουν λάβει την προτεινόμενη φροντίδα (57.2%) συγκρινόμενοι με ασθενείς με μέτρια (53.9%) ή ήπια (49.3%) νόσο (p=0.006). Κατ' αντιστοιχία, υψηλότερα ποσοστά συμμόρφωσης παρατηρήθηκαν σε ασθενείς με μικρή (<2 έτη) σε σχέση με υψηλή (≥2 έτη) διάρκεια νόσου (54.8% και 49.3% αντίστοιχα, p=0.02). Εμμένουσα ύφεση ή χαμηλή ενεργότητα επιτεύχθηκε σε 26.8% (95% CI 21.1% - 33.2%) των ασθενών, ενώ μείωση της κορτιζόνης σε δόση μικρότερη από 7.5 mg/ημερησίως και λήψη της συνιστώμενης δόσης υδροξυχλωροκίνης, επιτεύχθηκε σε 93.6% (95% CI 88.2% - 97.0%) και 73.5% (95% CI 66.6% - 79.6%) των ασθενών αντίστοιχα. Υψηλά ποσοστά συμμόρφωσης στους δείκτες ποιοτικής φροντίδας σχετιζόμενους με την παρακολούθηση, σχετίστηκαν με μειωμένο κίνδυνο για κάποια σύνθετη δυσμενή έκβαση (έξαρση νόσου, νοσηλεία ή συσσώρευση βλάβης) κατά το τελευταίο έτος παρακολούθησης (OR 0.97, 95% CI 0.96 - 0.99).

Στα πλαίσια αυτά, διερευνήθηκε το ποσοστό των ασθενών με υπολειπόμενη ενεργότητα νόσου κατά τη διάρκεια της τελευταίας επίσκεψης και κατά πόσο έγινε σε αυτούς αναβάθμιση της αγωγής. Από τα δεδομένα προέκυψε ότι 40% των ασθενών έχουν υπολειπόμενη νόσο και είναι δυνητικά υποψήφιοι για νέες θεραπείες. Οι περισσότερες αλλαγές στη θεραπεία έγιναν λόγω ενεργού νόσου στο νεφρό, στις αρθρώσεις ή στο

δέρμα, ενώ η προβλεπτική ικανότητα του SLEDAI-2K ως μέτρο ενεργότητας της νόσου ήταν μέτρια.

Συμπεράσματα

Δημιουργήσαμε δείκτες ποιοτικής φροντίδας για την αξιολόγηση καθώς και την βελτίωση της παρεχόμενης φροντίδας στους ασθενείς με λύκο. Παρά την εγκυρότητα των δεικτών ωστόσο, ο βαθμός συμμόρφωσης με αυτούς έχει μεγάλη διακύμανση και επομένως υπάρχει ανάγκη για περαιτέρω βελτίωση. Τα χαμηλά ποσοστά στους δείκτες, για τα καρδιαγγειακά και τη συμβουλευτική στην αναπαραγωγική υγεία, είναι συμβατά με δεδομένα από προηγούμενες μελέτες· τα ποσοστά για την προστασία από τον ήλιο, καθώς και κάποια μεμονωμένα στοιχεία σχετικά με την οστεοπόρωση και τους εμβολιασμούς (γρίπη, πνευμονιόκοκκος), είναι επίσης συμβατά με δημοσιευμένα δεδομένα. Διερευνώντας πιθανά αίτια σχετιζόμενα με καλύτερη εφαρμογή συγκεκριμένων δεικτών, βρέθηκε ότι η συμμόρφωση ήταν καλύτερη σε ασθενείς με διάρκεια νόσου μικρότερη από 2 έτη, καθώς και σε ασθενείς με σοβαρή νόσο. Αυτές οι παρατηρήσεις πιθανά υποδεικνύουν ότι η συμμόρφωση είναι καλύτερη αμέσως μετά τη διάγνωση, στην προσπάθεια των ιατρών να ελέγξουν τη νόσο, αλλά και όταν αντιμετωπίζονται ασθενείς με αυξημένη πιθανότητα να αναπτύξουν μη αναστρέψιμες βλάβες σε όργανα στόχους. Συνοψίζοντας, αναπτύχθηκε ένα σύνολο δεικτών ποιοτικής φροντίδας βασισμένων σε κατευθυντήριες οδηγίες της EULAR, μέσα από συστηματική ανασκόπηση της βιβλιογραφίας και αξιολόγηση από ομάδα ειδικών. Αυτοί οι δείκτες ποιοτικής φροντίδας μπορούν να χρησιμοποιηθούν ως μια σειρά από στόχους που πρέπει να επιτευχθούν, ώστε να αναβαθμιστεί η ποιότητα της παρεχόμενης ιατρικής φροντίδας και να εφαρμόζονται πληρέστερα οι κατευθυντήριες οδηγίες της EULAR.

INTRODUCTION AND RESEARCH QUESTION

1.SYSTEMIC LUPUS ERYTHEMATOSUS

A. EPIDEMIOLOGY

Systemic lupus erythematosus (SLE) is a chronic autoimmune multisystem disease with heterogenous clinical manifestations and a chronic relapsing-remitting nature. Young women are predominantly affected, with a female:male prevalence ratio 9:1. Greater prevalence and incidence of the disease is found in certain ethnic populations such as Black, Asian and Hispanic populations. Due to the chronic nature of the disease, combined with drug toxicity comorbidities and damage accrual, increased mortality has been observed compared to the general population.

There are reports, concerning last 5 years, on the incidence and prevalence of SLE, showing considerable variation across global regions or subpopulations. These differences are probably due to a combination of true variation with differences in study design and case definition.

The prevalence of SLE in Europe ranges between 29 and 210 per 100,000 individuals and has a greater variance than the estimated incidence. The incidence of SLE in Europe varies between 1.5 and 7.4 per 100,000 person-years, with data originating mainly from registries and subsequently from cohort studies. Registry based studies in the UK and Hungary, have reported an overall incidence of 4.9 per 100,000 person-years. Lower incidence rates have reported in France (3.3 per 100,000 person-years), Denmark (2.3 per 100,000 person-years) and Estonia (1.5 per 100,000 person-years) [1].

In Greece, according to the Greek National Organization for Provision of Healthcare Services electronic prescription platform (consisted of 7,742,629 Greek citizens, representing 72% of the total population), the prevalence of SLE was 0.075%, while in Crete a prevalence of 123 per 100,000 individuals, was reported. Concerning the

incidence of SLE, the highest one was reported in Crete (7.4 per 100,000 person years), while no data are published for the annual incidence overall in Greece.

Mortality rates across Europe, are about twice that of the general population, with cardiovascular disease and infections being the major causes. Patients with a younger disease onset, higher damage scores, or high cumulative doses of glucocorticoids, display higher mortality rates [2].

B. PATHOPHYSIOLOGY

SLE is caused by an autoimmune reaction in which the innate and adaptive immune systems organize an immune response towards nucleic acid containing cellular particles. It is characterized by the production of ANAs specific for nuclear antigens originating from uncleared apoptotic cells. However, the production of antibodies doesn't always lead to the development of SLE, taking into account that alot of people who have ANAs, do not reveal overt disease. The main determinants of this progression are environmentally induced defects, genetic abnormalities in immune cells and mutations in regulatory components involved in cellular apoptosis or defects in mechanisms of cellular debris clearance along with female sex [3,4,5].

Genetic factors

Two types of genetic factors that predispose to SLE have been described: low-frequency single gene mutations (more than 30 genes) with substantial impact on SLE susceptibility (monogenic SLE) and at least 100 genetic loci associated with SLE, which have a small effect on risk (polygenic, multifactorial SLE).

The SLE high- risk mutations are rare and include deficiencies in complement pathway gene products (C2, C4, C1q), which might contribute to SLE pathogenesis by impairing the clearance of cellular debris. Monogenic lupus is a form of SLE that typically presents early in life, with severe disease manifestations [6,7].

SLE genetic variants represent regulatory events rather than coding sequences and a common theme is that they encode proteins implicated in important molecular pathways that alter immune function. More precisely the pathogenetic roles of SLE-associated genetic variants are: i) activation of the innate immune system, with increased type I interferon production, increased response to type I interferon and altered antigen presentation, ii) dysfunction of the adaptive immune system, with altered lymphocyte signalling, altered lymphocyte differentiation and increased levels of lymphocyte factors,

iii) increase in availability of self-antigens, with impaired nucleic acid degradation, increased cell death and impaired cell debris clearance [6].

Environmental risk factors

Apart from age, sex and genetics, it is currently known that different environmental factors could trigger SLE onset and flares in genetically susceptible individuals [8]. A family history of SLE or related autoimmune diseases, increases the risk of SLE, however GWAS studies estimate that genetic risk factors only account for ~30% of observed heritability. This percentage matches with the low to modest concordance rates observed in monozygotic twins (with SLE at as low as 24%) which highlight the contribution of environmental factors in SLE pathogenesis [9,10,11]. Several exogenous exposures have been suggested to influence risk of SLE, which more precisely are:

1. *Crystalline silica dust*: There are three population-based, case-control studies of SLE from the South-eastern United States [12], Boston [13] and Canada [14], where evidence of the contribution of silica exposure to the development of SLE, is provided [15]. Two studies in lupus- prone mice reported increased autoantibodies and immune complexes contributing in the development of glomerulonephritis, when exposed to silica [11,16,17].
2. *Cigarette smoking*: Several studies support a positive association between current smoking of cigarettes and overall SLE risk, based on DNA damage and autoantibody production [9,11]. Two metanalysis of 12 and 9 studies respectively, revealed that current smokers were more likely to develop SLE compared to lupus patients who had never smoked [18,19], while current smokers presented with increased ds-DNA (+) SLE in a large cohort of US women [20].
3. *Pesticides*: It is difficult to ascertain specific exposure due to diverse active ingredients among various pesticides and due to dramatic changes in the

available products and formulations over the decades. Furthermore, older organochlorine insecticides, no longer in use, persist in the environment, so exposures are not easily self-reported. Two studies have reported that pesticide exposure, both agricultural and residential is associated with increased SLE risk [9,21].

4. *Organic pollutants*: Dioxins, furans, PCBs, have varying mechanisms of biological activity and toxicity including immunosuppressive effects of dioxin-like compounds. Increased SLE mortality (starting 10 years after exposure) was observed in long- term follow-up of a Taiwanese population exposed to high levels of organic pollutants through consumption of contaminated rice [9,11,22].
5. *Heavy metals:* Experimental studies in animal models suggest that heavy metals increase the risk of systemic autoimmunity, however there is lack of evidence for human population [11,23]. Limited data suggest association between SLE and uranium exposure, with increased antichromatin or ds-DNA antibody levels. Concerning mercury exposure retrospective studies have revealed increased SLE risk [24,25].
6. *Infections:* They include viral, bacterial, parasitic and fungal infections. Bacterial infections can expose the immune system to host nuclear material due to direct cell death or to bacterial DNA due to bacterial death. These autoantigens lead to the production of autoantibodies, but they also represent PAMPs of viruses and bacteria and DAMPs of host nucleic acids, which activate innate immunity [26]. Concerning viruses, they are classified in two categories: endogenous and exogenous viruses. The first category includes HERVs which may be responsible for the loss of immunological tolerance and the triggering of SLE. The second category includes EBV, CMV, HIV and Parvovirus B19 [27].
7. *UV radiation:* UV irradiation induces cellular damage and stimulates the release of proinflammatory factors from mast cells, which are increased in number within cutaneous lesions. In a prospective study, in patients with SLE who were

exposed in UV light, skin lesions developed and upregulation of interferon-related and MHC-related genes was observed in the skin of patients [28].

8. *Hormonal factors:* In mouse models addition of oestrogen or prolactin can lead to an autoimmune phenotype with increased autoreactive B cells, posing important questions concerning the use of oral contraceptives or hormone replacement therapy. Although hormones can influence murine models, the use of oral contraceptives does not increase disease flares in stable disease [4].

Innate immune system

Increases in the apoptotic cell load can be generated by exposure to environmental triggers. Apoptotic cells are cleared mainly by cells of the reticuloendothelial compartment. Persistent and increased apoptotic debris containing nucleic acids and immune complexes, can stimulate an inflammatory response through the activation of TLRs, due to an inability of being completely cleared. TLRs (3, 7, 8, 9) are located in in the endoplasmic reticulum (of B cells, some T cells, dendritic cells, and macrophages, as well as non-immune cells such as epithelial cells and fibroblasts) and move to early endosomes where TLRs 9 (which senses DNA) and 7 (which senses single- stranded RNA) drive a strong IFN response along with proinflammatory cytokines. They also play a central role in loss of tolerance.

Concerning proinflammatory response, many cytokines are elevated in SLE, performing variable functions. The most important cytokines are IFN I, TNF, IL-6, IL-10, IL-17 and BAFF. BAFF is a B cell activating factor also known as BLyS, whose levels are increased in patients with SLE and positively correlate with autoantibody titers.

The major cell types involved in innate immunity of SLE are dendritic cells, myeloid cells and macrophages. Regarding dendritic cells, SLE patients have a reduced number of circulating conventional dendritic cells and an increased number of plasmacytoid dendritic cells which are particularly responsible for type I IFN secretion via TLR 7 and

9. On the other hand, the representative of myeloid cells are neutrophils. Neutrophils are short-lived representing the major cause of increased apoptotic cell load. In addition, patients with SLE have an abnormal subset of neutrophils with increased potential for NETosis and reduced production of reactive oxygen species (altering apoptotic pathway). NETosis is a mechanism of cell death where extrusion of chromatin, nuclear, cytoplasmic and granular material takes place. In the extrusion material are also contained proinflammatory cytokines, antimicrobial peptides, antigenic anticitrullinated histones and dsDNA contributing to the stimulation of IFN I production by plasmacytoid dendritic cells [6,29]

Adaptive immune system

Participation of adaptive immune system in SLE pathogenesis includes deficiencies or alteration in T cell signaling, in production of cytokines, in proliferation or regulatory functions. More precisely, T cells are the main contributors of B cell differentiation. T cells from patients with SLE express CD40L (costimulatory molecule) for a longer period than healthy T cells, as a result, the activation and differentiation of B cells is increased. Also, T follicular helper cells which promote differentiation of antibody- producing B cells are expanded in SLE, as long with a loss of peripheral T cell tolerance and deficiency of T regulatory cells (which have the ability to suppress immune response). Finally, IL-2 production which is important for the maintenance of T regulatory cells, is impaired therefore leading to T regulatory deficiency.

B cells contribute to pathogenesis through their responses to antigen, regulation of other cells, autoantibody production and increased antigen presentation to T cells. Autoantibodies result from immune complexes which activate complement and induce inflammation. However, the pathogenetic key in participation of B cells is loss of tolerance through their activation via TLRs and stimulation by BAFF. Early immature B cells show increased autoreactivity in SLE, possibly due to loss of central tolerance in thymus [6,29].

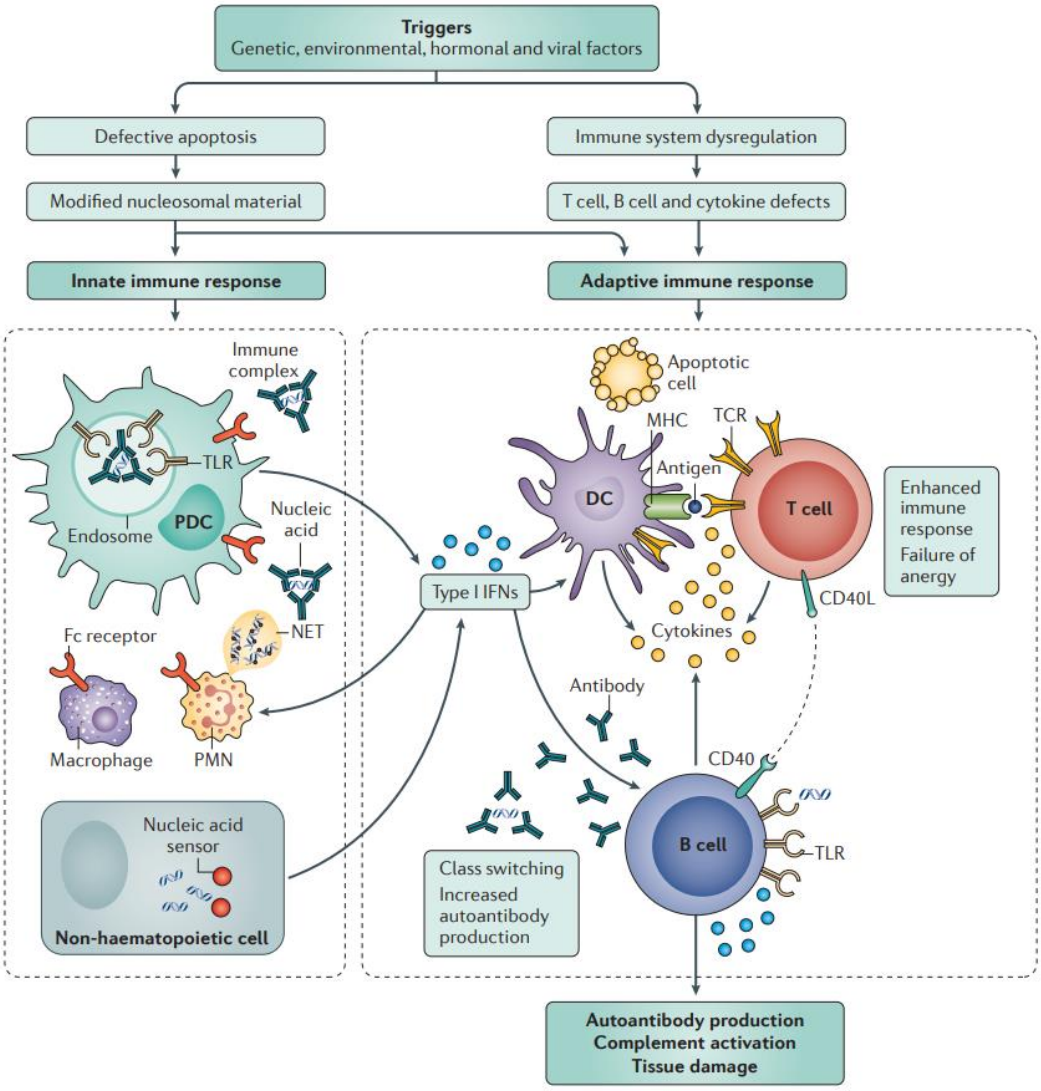

Figure 1 *Immune dysfunction in SLE, Nat Rev Dis Primers 2016, Systemic lupus erythematosus*

C. CLINICAL MANIFESTATIONS, DIAGNOSIS AND NATURAL HISTORY OF SLE

Clinical manifestations

SLE is a complex autoimmune disease with variable clinical features. According to the dominant organ involved, SLE can present with manifestations from the skin, kidneys, central nervous system, blood, heart, lungs and musculoskeletal system. It can also present with serositis, antiphospholipid syndrome or constitutional symptoms such as fever.

Skin involvement occurs in about 90% of patients with SLE and the key characteristic is its photosensitive distribution. It includes acute cutaneous lupus (malar rash or generalized maculopapular rash), subacute cutaneous (which occurs as two major clinical forms: 1. annular or plycyclic and 2. papulosquamous- psoriasiomorf cutaneous eruption, usually photodistributed) and chronic cutaneous or discoid lupus (erythematous- violaceous cutaneous lesions with secondary changes of atrophic scarring, dyspigmentation, follicular hyperkeratosis leading to scarring alopecia on the scalp). If skin biopsy is performed typical changes must be present. Other rare variants include bullous acute lupus erythematosus or Rowell syndrome with erythema multiforme- like target lesions. In addition to specific skin lesions, non-specific skin lesions may exist, such as livedo reticularis, periungual telangiectasias, Raynaud's phenomenon and alopecia [28,30,31].

Musculoskeletal involvement takes place in about 90% of patients, including either a) synovitis involving two or more joints characterized by swelling or effusion or b) tenderness in two or more joints with at least 30 minutes of morning stiffness [30,31].

Involvement of the mucous membranes occur in ~25% of SLE patients and is usually presented with irregularly shaped raised white plaques, areas of erythema, silvery white

scarred lesions and ulcers with surrounding erythema on the soft or hard palate or buccal mucosa [4].

Kidney disease develops in up to 40% of patients with SLE, representing a major cause of morbidity. Most patients with SLE who develop lupus nephritis present with clinical manifestations within 5 years of SLE diagnosis. Furthermore, 5-20% of patients with lupus nephritis develop end-stage kidney disease within 10 years from the initial event. Lupus nephritis is a form of glomerulonephritis and is histologically classified into six distinct classes (I-Minimal mesangial, II-Mesangial proliferative, III-Focal proliferative, IV-Diffuse proliferative, V-Membranous, VI-Advanced sclerotic) each of them representing different manifestations and severity. The clinical presentation and laboratory findings may differ ranging from silent lupus nephritis to severe proteinuria and nephrotic syndrome or acute nephritic syndrome. According to the class of glomerulonephritis, treatment is determined [31,32].

Multiple clinical manifestations have been associated with neuropsychiatric SLE (NPSLE). The central nervous system manifestations range from subtle cognitive dysfunction, to acute confusional states, psychosis (characterized by a) delusions and/or hallucinations without insight and b) absence of delirium) seizure disorders (primary generalized seizure or partial/focal seizure) and stroke. Although headache, mood disorders, anxiety and mild cognitive dysfunction are the most frequent complaints, they do not usually reflect disease activity in the CNS. On the other hand, cerebrovascular disease, seizures, acute confusion, neuropathies and myelitis are the most typical presentations of NPSLE [30,31,33].

Hematological abnormalities are common findings in patients with SLE and include leukopenia, thrombocytopenia and autoimmune hemolytic anemia. Leukopenia is defined as $<4000/mm^3$ on two or more occasions, with lymphopenia ($<1.5 \times 10^9$ lymphocytes/L) being the most frequent. Although leukopenia occurs in ~50-60% of patients with SLE, only 17% have a WBC count<1000/mm. Thrombocytopenia is a

platelet count <100.000/mm^3, without any other identifiable cause. Autoimmune hemolytic anemia may present with constitutional signs or symptoms, while the patients may display concomitant or sequential thrombocytopenia (Evans syndrome). Therefore, monitoring for the development of thrombocytopenia is important [34].

Pulmonary manifestations of the disease include diseases of the lung parenchyma, pleura and pulmonary vasculature. Lung parenchyma disease includes interstitial lung disease which is relatively uncommon in SLE and acute lupus pneumonitis (in 1-4% of SLE patients). Pleural involvement is the most common SLE-related lung disease (30-50% of patients) and the diagnosis is clinical with typical features in patient's history. Finally, disorders of the pulmonary vasculature include pulmonary arterial hypertension (~8%), pulmonary embolism and diffuse alveolar hemorrhage (<5%) [35].

Natural history and disease patterns

In Western countries, the all-cause and cause specific standardized mortality rate of SLE patients, has significantly decreased over time. In the late 1940s, over 40% patients with SLE died within 3 years of onset of first symptoms. Since then, the 5- and 10-year survival of SLE patients has remarkably improved to over 90%. However, mortality rates are particularly high for patients aged less than 40 years. After a period of major improvement, survival in SLE has plateaued since the mid-1990s, while disparities in SLE mortality persist according to sex, race, age and place of residence. In high- income countries, 5-year and 10-year survival exceeds 95%, while in low-income countries survival is lower [36,37].

SLE is characterized by an extremely variability of disease expression, both between individuals and within individuals over time. Persistent disease activity over time is one of the major causes of morbidity and mortality in patients with SLE [38]. Therefore, it's important to understand the burden of disease activity over time by defining the patterns of disease activity. Three main approaches have been proposed since 1999. Barr *et*

al first described patterns of disease activity, measured prospectively over time (204 patients with at least two years of regular follow up) and analyzed the frequency of these different patterns. Three disease activity patterns were identified: a) Relapsing-remitting: periods of disease activity interspersed with periods of disease inactivity on ≥2 visits, b) Chronic active: disease persistently active (M-SLEDAI and PGA >0) for at least 1 year and c) Long quiescent: disease that has remained quiescent (M-SLEDAI=0, PGA=0 or a single PGA value<1) for at least 1 year [39]. Disease activity patterns were also described by Gyori *et al* in a prospective study (2386 patients with at least one year of regular follow-up) and were: a) Persistent relapsing-remitting: 3 consecutive years of relapsing- remitting pattern with at least 1 flare per year, b) Persistent chronic active: 3 consecutive years of chronic active disease and c) Persistent long quiescent: 3 consecutive years of long quiescent pattern [38]. Finally, in Tselios *et al* study (267 patients with at least 10 years of follow-up), a new nomenclature for disease patterns was introduced, including: a) Relapsing- remitting: at least two periods of clinical remission following periods of activity, while a remission period was defined as two consecutive visits with a clinical SLEDAI-2K=0, b) Persistently active: patients who had never achieved a period of clinical remission, c) Prolonged remission: clinical SLEDAI-2K=0 for at least 10 consecutive years [40]. In the two of the studies, relapsing-remitting course was the most prevalent pattern (70%, 54% respectively), while complete remission was less frequent pattern in all of the three studies (7%, 10%, 25%).

Strategy trials in rheumatoid arthritis had revealed the utility of a low disease activity state definition, as a foundation of treat-to-target approaches, given the fact that rates of complete remission are generally low. Therefore, there was a need for the definition of a low disease activity state in SLE also, so LLDAS was recently generated (SLEDAI-2K≤ 4, no activity in major organs, PGA≤ 1, current prednisolone dose ≤ 7.5mg daily, well tolerated maintenance doses of immunosuppressive drugs) [41]. Validation of

LLDAS have shown halting in damage accrual and prevention of flares in comparable rates with complete remission [42].

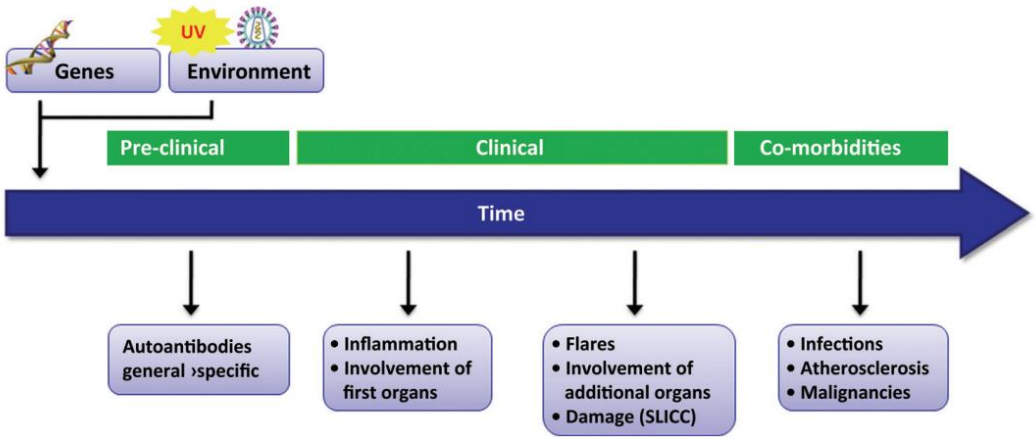

Figure 2 *Natural history of SLE, Ann Rheum Dis 2010, Therapeutic opportunities in systemic lupus erythematosus: state of the art and prospects for the new decade*

D. METROLOGY, FLARE AND DAMAGE DEFINITION

Due to the multiorgan involvement, there is a need for use of both global and organ-specific, validated disease activity indices to guide therapy and to serve as outcome for clinical trials. The three most widely used indices are: a) SLEDAI, b) BILAG, c) SELENA-SLEDAI PGA. These scores take into account general signs and symptoms in various organs, while SLEDAI also scores serological features. PGA is a subjective score which complements objective activity indices and is more sensitive to longitudinal changes. In our practice SLEDAI-2K version of SLEDAI is used, in combination with PGA.

Concerning lupus flares there is a variety of definitions. According to Lupus Foundation of America, flare is a measurable increase in disease activity in one or more organ systems involving new or worse clinical signs and symptoms and/or laboratory measurements. It must be considered clinically significant by the assessor and usually there would be at least consideration of a change or an increase in treatment. On the other hand, SELENA-SLEDAI flare is defined by changes in SLEDAI score and/or individuals manifestations and/or changes in treatment and/or need for hospitalization and or changes in PGA. Finally, SLEDAI flare is defined by clinical important changes and increase of the score>3 [36,43].

Finally, it's important measuring organ damage because of its association with adverse clinical outcomes and death. The score used for this purpose is the SDI which measures irreversible damage accrual in 12 organ systems. Damage accrual is due to either disease or medication side effects and the items that are scored must be present for at least six months [36,42].

E. COMORBIDITIES

Cardiovascular disease

SLE is associated with increased risk for accelerated atherosclerosis and cardiovascular events including coronary heart disease, cerebrovascular and peripheral artery disease. Cardiovascular events occur both early and late during the disease course, with younger patients being at much higher risk than age-matched counterparts [44]. Factors such as diabetes, hypertension and hyperlipidemia, can be exacerbated by glucocorticoids, other lupus therapies as well as disease activity [45]. For blood pressure and cholesterol regulation the targets for general population should be considered.

Infections

Infections are a significant cause of morbidity and mortality in SLE. The net risk of infection in SLE is associated with both disease-related and treatment-related factors. The most common infections in SLE are pneumonia and bacterial sepsis, with *Staphylococcus aureus, Streptococcus pneumoniae and Escherichia coli* as the most common causative agents. There is also a 2.5 fold higher risk of herpes zoster in comparison to general population.

Concerning infection prophylaxis with vaccination, patients ought to receive vaccinations according to the EULAR recommendations and vaccination status or indications for further vaccination should be assessed yearly. Also, vaccination must be preferably administered during stable disease, and prior to planned immunosuppression, in particular if B cell depleting therapy is considered as treatment plan (at least 6 months after the administration and 4 weeks before the next course of B cell depleting therapy). Non-live vaccines can be administered to SLE patients while treated with systemic glucocorticoids or DMARDs [36,46,47].

Malignancies

According to observational studies and epidemiologic evidence, patients with SLE are at an increased risk of developing cancer. More precisely there is an increased risk of lung, liver, cervical, vulvovaginal, thyroid, hematological cancer and lymphomas. The risk for lymphoma is increased approximately threefold. On the other hand, the risk of breast and prostate cancer is decreased. A meta-analysis which includes 48 cohort studies involving 247,575 patients, demonstrates that patients with SLE have a 62% overall cancer morbidity and a 52% cancer related death [36,48].

F. MANAGEMENT AND TREAT-TO-TARGET STRATEGY

SLE is a challenge concerning diagnosis and treatment due to its multiorgan manifestations. Treat-to-target strategy should be taken into account, when efforts are made to determine the goals of treatment. The most important treat-to-target principles include a variety of parameters. SLE treatment should aim at complete remission of systemic symptoms and organ manifestations, which in other words means, absence of clinical activity with no use of glucocorticoids and immunosuppressive drugs (SLEDAI=0, under hydroxychloroquine). However, due to low rates of complete remission, LLDAS is the next target to be achieved given the fact that it has shown reduced damage accrual and prevention of flares in comparable rates with remission. In addition, prevention of flares is also an important therapeutic goal as well as prevention of damage accrual. Finally, early recognition ant treatment of renal involvement is strongly recommended, because delay in diagnosis and treatment has been associated with increased risk for renal relapses and ESRD.

Concerning treatment of SLE patients, hydroxychloroquine is recommended for all patients with SLE, at a dose not exceeding 5mg/kg. Goal treatment in long-term glucocorticoid therapy should aim to minimize daily dose to ≤7.5mg. To achieve this goal in chronic stable disease, immunomodulatory agents such as methotrexate, azathioprine or mycophenolate can be used as maintenance therapy. In flares, persistent-active or organ-threatening disease, pulses of intravenous methylprednisolone along with initiation of drugs such as cyclophosphamide and biological therapies (rituximab, belimumab, anifrolumab) can be initiated [36,42,49].

2.QUALITY INDICATORS

A. QUALITY OF CARE - BRIEF HISTORICAL RECURSION

The quality movement within hospital settings has a long history, spanning over at least three decades. The issue of patient safety has been recognized increasingly as a substantial element of overall quality, and researches have taken place worldwide, with the United States being the pioneer in this area. The story begins in 1966, with the physician Avedis Donabedian who first published a paper entitled: “Evaluating the Quality of Medical Care”, creating a framework, which provides the basis for the current methods used to evaluate healthcare quality. This study was followed by the establishment of the IOM in 1970, and the AHRQ, in 1989, both of them, aiming at the improvement of quality of care.

Three studies that have been published are considered to be of fundamental importance. The first was the Harvard Medical Practice Study in 1991, which showed that adverse events occurred in 3.7% of hospitalizations and that 27.6% of the adverse events could be attributed to errors [50]. The second, *To Err is Human: Building a Safer Health System*, published by the US IOM in 1999, resulted in increased awareness of U.S. medical errors. This report was based upon analysis of multiple studies by a variety of organizations and concluded that 44,000 to 98,000 people die each year as a result of preventable medical errors. This figure was greater than the number of deaths attributed to motor vehicle accidents (43 458), breast cancer (42 297) or AIDS (16 516) [51,52]. The third, *Crossing the Quality Chasm: A New Health System for the 21st century,* was published in 2001, again by IOM, and focuses more broadly on how the health system can be reinvented to foster innovation and improve the delivery of care. Towards this goal, an action plan was developed, based on six characteristics that health care quality should have (be safe, effective, patient-centred, timely, efficient, equitable) [53].

B. DEFINITIONS

There are several definitions of health care quality. The most widely used is the definition of IOM, introduced in 1996. According to the latter, health quality care, is “the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge”. The definition applies to health care practitioners and to all settings of care (hospitals, nursing homes, physician’s offices), as well as to interactions between healthcare providers and patients in different stages of a patient’s journey. Researchers measure health care quality to identify problems caused by overuse, underuse or misuse of health resources [54].

With regard to the definition of health care quality, the latter can be approached and interpreted through a conceptual model, referring to the three levels of health care here below. This model called the *Donabedian model*, was firstly described by Avedis Donabedian in 1966 and includes:

a) Structure: Denotes the attributes of the settings in which care occurs. This includes the attributes of material resources (facilities, equipment, money), of human resources (number and qualifications of personnel), and of organizational structure (such as medical stuff organization).
b) Process: Denotes what is actually done in giving and receiving care. It includes the patient’s actions in seeking care, as well as the practitioner’s actions in making a diagnosis and recommending or implementing a treatment. In other words, process is divided into technical quality (including the provision of care that adheres to recommended guidelines) and interpersonal quality (including the interaction between physician and patient, which is the vehicle by which the application of technical care is achieved).
c) Outcome: Denotes the effects of care on the health status of patients and populations. Improvements in the patient’s knowledge and changes in the

patient's behaviour are included under a broad definition of health status, and so is the degree of the patient's satisfaction with care [55,56]

The three-part assessment approach describes a linear relationship and is based on the idea that a good structure increases the probability of a good health care processes, and in turn, good care processes increase the probability of good outcomes. Importantly, for a process to be a valid measure of quality, it must be closely related to a result that people find satisfactory and important (fig.3)

Figure 3 *Levels of healthcare measurement*

Complementary to IOM's definition, the WHO adds that in order to "achieve desired health outcomes, health care must be safe, effective, timely, efficient, equitable and people-centred". These six conditions tend to be the most important measurable aspects of health care, constituting the basis upon which quality measures can be developed. In relation to the six-dimensional approach concerning health care quality, the EXPH in 2014, defined five key dimensions that all health care services should have, regardless of the level of care: effectiveness, safety, appropriateness, patient-centeredness, and efficiency/equity [57]. The specific definitions of these items are represented here below (Table 1).

The dimensions of quality as defined by the WHO Vs the EU EXPH	
WHO	**EU EXPH**
***Effective*:** Delivering health care that is adherent to an evidence base and results in improved health outcomes for individuals and communities, based on need	***Effective*** and improving health outcomes
	Appropriate and complying with current professional knowledge as well as meeting agreed standards
Efficient: Delivering health care in a manner which maximizes resource use and avoids waste	***Efficient*** and ***equitable*** leading to the best value for the money spent and to equal access to available care for equal need, utilization and equal quality care for all
Equitable: Delivering health care which does not vary in quality because of personal characteristics such as gender, race, ethnicity, geographical location, or socio-economic status	
Accessible: Delivering health care that is timely, geographically reasonable and provided in a setting where skills and resources are appropriate to medical need	
Acceptable/patient centred: Delivering health care which takes into account the preferences and aspirations of individual service users and the cultures of their communities	***Patient-centred*** and involving patients/people as key partners in the process of care
Safe: Delivering health care which minimizes risks and harm to service users	***Safe*** and preventing avoidable harm related with care

Table 1 *Source: European Patients Forum, Position Paper on Quality Care, 2017*

C. QUALITY MEASURES

General steps and rationale of Quality Indicators development

Due to the recognition that quality of care is suboptimal, measures for the assessment of quality care, started to emerge. The most commonly used tools to measure the degree of quality of care that patients receive, are QIs. QIs are a set of quantitative measures that can be related to the structures, processes or outcomes of care, based on the Donabedian model that was presented above [56]. They usually emerge from guidelines, systematic literature reviews, or expert panel consensus through the use of a systematic approach and they represent the current standard of care. In contrast to most guidelines or recommendations, QIs pertain to measurable aspects of health care- they describe exactly who should do what and when, with respect to disease monitoring. Thus, QIs highlight potential quality concerns, identify areas that need further study and investigation, track changes over time and aim at quality improvement [58,59,60].

There are several groups, including the NQF, IOM, NCQA, AHRQ, NICE, that have developed frameworks describing the general steps and rationale that should determine quality measures.

A representative model for developing QIs, is described from AHRQ, which in general includes:

a) Identification of candidate indicators, which includes systematic review of the literature along with expert opinion, in order to form a conceptual model of each QI.
b) Evaluation of the proposed QIs based on the criteria of importance, scientific acceptability, usability and feasibility (according to NQF evaluation criteria). More precisely, importance refers to the extent that the specific measure is evidence-based, while scientific acceptability includes the notions of reliability and feasibility both of which describe the extent to which the measure produces

consistent (reliable) and credible (valid) results about the quality of care. Validity demonstrates that the data elements are correct and consistent with the current evidence, while reliability demonstrates the extent to which data elements are repeatable. Feasibility describes the extent to which the specifications, including measure logic, require data that are readily available or could be captured without undue burden and can be implemented for performance measurement. Finally, usability refers to the extent to which potential audiences are using or could use performance results in order to achieve the goal of high-quality, efficient healthcare for individuals or populations (fig.4) [60].

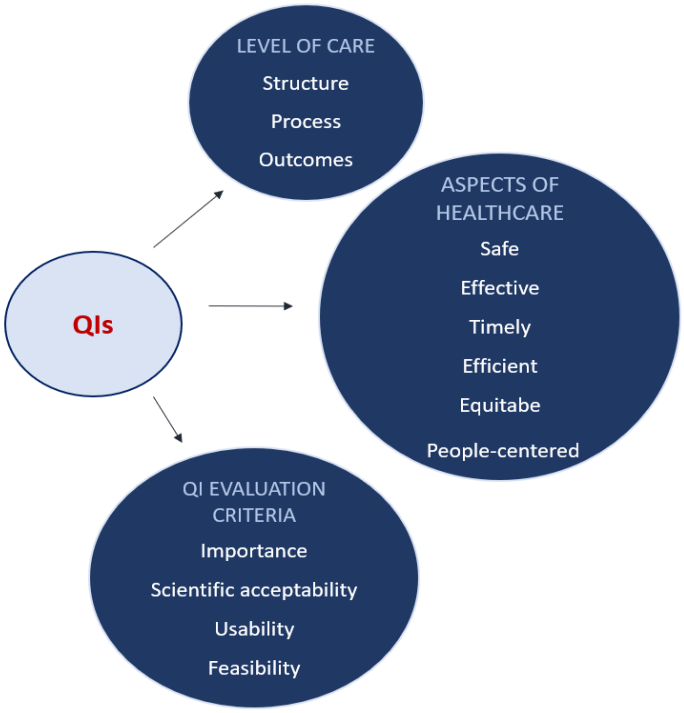

Figure 4 *The 3 axes upon which QIs are formed*

Classification of QIs

As previously mentioned, QIs are classified into three categories, according to the level of healthcare they are intended to measure. Structural indicators describe the type and amount of resources used by a health system or organization to deliver programs and services, and they relate to the presence or number of staff, clients, money, beds, supplies, and buildings. Process indicators assess the type and quantity of care that is provided, in other words what the provider did for the patient and how well it was done. Outcome indicators capture the effect of care processes on health, such as recovery from an illness, death, complications of healthcare and health status. Due to various factors that affect the patient's survival and health outcomes, it's important to mention that risk adjustment for these measures should take place, allowing fair comparisons [61,62].

For many chronic diseases, quality assessment has focused primarily on process rather than outcome measures due to the fact that health outcomes often require years to develop so their measurement may therefore delay timely interventions, and also, due to the fact that there is limited consensus on the correct outcome measures to assess many conditions. Perhaps, as a result of these limitations, QI sets pertaining to several prevalent rheumatic diseases have also focused on process measures [63].

Quality Indicators in SLE

SLE is a multisystem disease with considerable morbidity due to both the disease per se and the complications of chronic treatment. In addition, due to its variable manifestations, SLE requires care by multiple providers, leading to a fragmented structure of care and potential deficiencies in quality. Based on the general hypothesis that better quality of health may lead to better outcomes, improved quality of health care could reduce negative outcomes and disease burden, in SLE as well. In 2009, Yazdany et al., were the first that undertook the initiative with regard to QI set development, due

to the lack of consensus on health care processes which could have facilitated research on quality of health care received by SLE patients. More precisely, a systematic review of guidelines, recommendations and literature was performed in order to develop a set of 29 QIs which subsequently were rated in terms of validity and feasibility. Finally, a set of 20 QIs had been formed, including domains of diagnosis, general preventive measures (sun avoidance, vaccinations), osteoporosis, drug monitoring, renal disease, cardiovascular disease, pregnancy and reproductive health counseling [63]. The next QI set was formed in 2011 by Mosca et al. A preliminary set of 15 QIs was initially developed based on EULAR recommendations for SLE, which, after Delphi survey, ended up in a set of eleven QIs. In comparison to the initial QI set (Yazdany et al.), QIs for infection screening and for disease activity and damage assessment were added [59].

Apart from developing QIs, evaluation of their performance on SLE patients is significant in order to measure the gap between guidelines and clinical practice, identify areas that need further study and investigation and track a potential association with disease outcomes. The first publication concerning performance evaluation of 13 QIs included data from a prospective, longitudinal study of 814 individuals. QI performance varied from 29% with assessment of cardiovascular risk factors to 90% with sun avoidance counseling, while overall compliance rate was 65%. Younger patients were less likely to receive services including vaccinations, drug toxicity and cardiovascular risk assessment. Also, patients having fewer physician visits and lacking health insurance were significantly associated with lower QI performance [64]. Two years later a second publication with 737 participants, spanning from 2009 to 2013, was carried out. Relationship between high performance (receipt ≥85%) on 13 validated quality measures, and disease outcomes, was examined. The participants were eligible for a mean of five quality measures, while the overall quality measure pass rate at baseline was 64%. The pass rate was not associated either with year-to- year or a long-term

increase in disease activity, with or without adjustment for covariates. However, a pass rate ≥85% was strongly protective against a clinically significant increase in disease damage, demonstrating a link between processes of care and important outcomes [65]. Also, a cross-sectional analysis of a German long-term study with 580 patients took place in order to measure the quality of care provided to SLE patients, understand potential gaps and analyze association with outcomes. In total 10 aspects of care were analyzed and performance varied between 22.8% for lipid metabolism counseling and 97.6% for dose of glucocorticoids and osteoporosis prevention. Also, higher performance on the clinical care parameters was predictive for low progress in disease-related damage and low disease activity. Osteoporosis prevention and antimalarial treatment had the greatest impact on damage, while the blood pressure counseling and osteoporosis prevention had the greatest impact on lowering disease activity [66].

UNMET NEEDS IN SLE CARE AND RESEARCH OBJECTIVES FOR THIS THESIS

SLE requires care by multiple providers, leading to a fragmented structure of care and potential deficiencies in quality. Based on the general hypothesis that better quality of health may lead to better outcomes, improved quality of health care could reduce outcomes and disease burden, in SLE as well. QIs, have been proposed for SLE, but for the most part they were not based on a comprehensive systematic literature review.

To this end we sought to develop the first comprehensive set of QIs in SLE based on an extensive SLR of the various aspects of SLE, performed as part of the 2019 EULAR recommendations for SLE. This study capitalises on this work by developing QIs to detect potential gaps in SLE care and facilitate the implementation of the guidelines. Importantly, we sought to test them in real life. Initial real-life data suggest a variable degree of adherence to the recommendations and identify areas for further improvement.

Concerning clinical impact, QIs can be used towards assessing and improving patient care. They may facilitate the implementation of the EULAR recommendations by creating a checklist to be used towards detecting gaps in lupus care and facilitating efforts towards remedying them.

As a spin-off this work, we also sought to determine the proportion of SLE patients with residual disease activity during their most recent visit, and whether patients with residual activity were offered therapy intensification. Our data suggest that about 40% of patients have evidence of residual disease activity and could qualify for novel treatments. Most treatment changes were triggered by active renal, joint, and skin disease, whereas the predictive value of SLEDAI-2K as a metric of disease activity was modest.

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RESULTS AND PUBLICATIONS