GENERAL PRINCIPLES IN THE MANAGEMENT OF GLOMERULAR DISEASE

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Disclosure of Interests

Compensated Consultant to:

Genentech-Roche, Bristol-Myers Squibb, Chemocentryx, Achillion, Omeros, Apelliis, Sanofi-Genzyme, Mallinkrodt (Data Monitoring Committees, Advisory Boards)

Speakers Bureau

Genentech

Editor

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Outline of Presentation

- Chapter 2- KDIGO-GN (2012)- Topic Headings
- Analysis of 2012 Topics and highlighting possible revisions of content
- Suggested New Topic Headings
- Conclusions and Reccomendations
- Adaptiv CPG incorporating SCAMPS

GENERAL PRINCIPLES:
Overview

- These are *over-arching* statements that apply broadly to many or all of the specfic conditions to be analyzed by an evidence-based Clinical Practice Guideline (CPG)

- Applications of or specific *exceptions* to these general principles and the relevant rationales are delegated to the individual Chapters of a CPG

- The evidence underlying these General Principles varies widely and remains largely *Ungraded or Non-Cited*

GENERAL PRINCIPLES

Topic Headings

(KDIGO-2012- Cattran and Feehally)

- **Kidney Biopsy**
- **Assessing Kidney Function**
- **Outcome Measures**
- **Impact of Age/Gender/Ancestry**
- **Management of Complications/Risk Avoidance**
- **Adverse Effects of Therapy**
- **Therapeutic Agent Monitoring**
- **Pregnancy**
- **Costs**
- **Post-Transplant Recurrent Disease**
- **Research Recommendations**

GENERAL PRINCIPLES:
Renal Biopsy

- **Indications/Contraindications/Technique/Specimen Adequacy/Risk of Complications**

- **Analysis requirements (LM, special stains, IF, EM, LD-MS, antigen identification and rescue) – defining the minimum and optimal by specific disease**

- **Scoring methods and classfication criteria (when available; e.g.OXFORD-MEST-C). Emphasis on *disease diagnosis and pathogenesis not „pattern of injury“***

- ***Protocol or By-indication* repeat renal biopsies**

GENERAL PRINCIPLES:
Assessment of Kidney Function

- ***Proteinuria (Albuminuria)*: Methods, Sources of error, Pitfalls, Albuminuria vs Total Protein, 24 hour vs untimed collections; Ratios (corrected and uncorrected for creatinine generation (UPCR/UACR). Protein selectivity (e.g. FEIgG); Beta2 microglobulinuria**

- **Uniform Definition of *Nephrotic Syndrome and Nephrotic-Range Proteinuria***

- ***Estimation of GFR:* Equations, Biomarkers, Pitfalls and Limitations, Influence of Diet, Drug (e.g. Steroids)Sarcopenia, Obesity/Weight Loss; role og mGFR confirmation in clinical trials**

GENERAL PRINCIPLES:
Outcome and Prognosis Measures

- ***Definitions of Remissions*** **(Disease Specific): Proteinuria (Time-averaged or other), hematuria and eGFR/mGFR (slope, abolute change)**

- ***Definition of ESRD*****: Competing risks, CV vs all-cause**

- ***Estimation of GFR :*** **Pitfalls and Limitations;*slopes, time to event, % change from BL.* New Biomarker panels, Point-of-care mGFR;**

- **Definitions of *Futility and Point–of–no-Return – Disease-specific***

- ***Quality of Life; Extension of Life Expectancy***

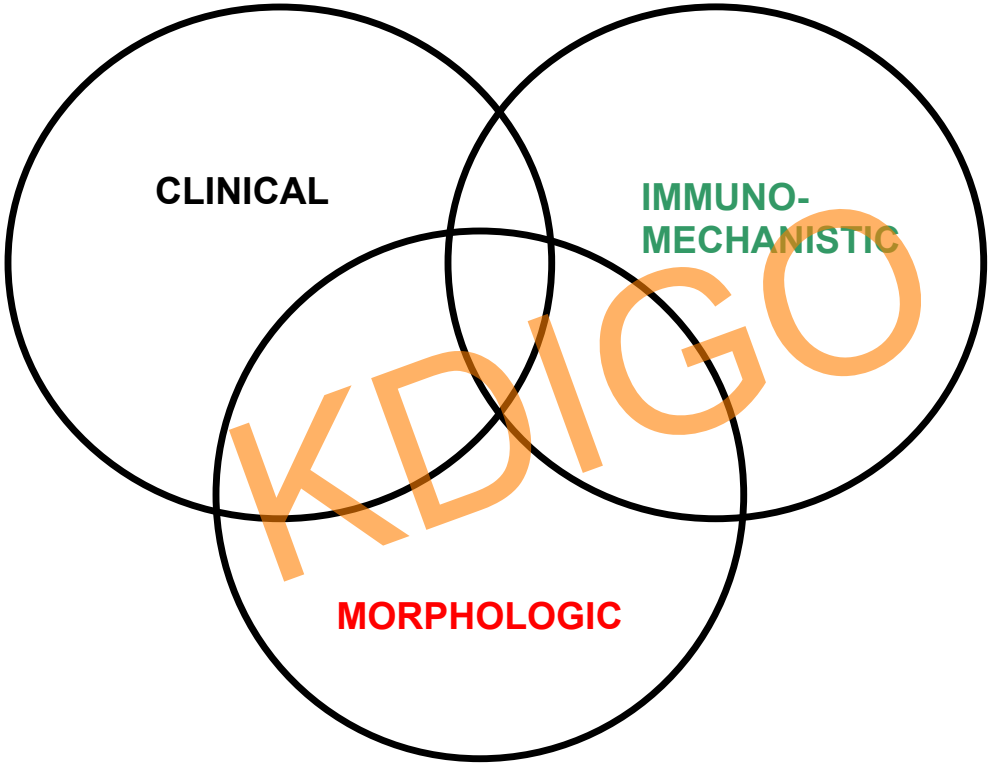
GENERAL PRINCIPLES:

Proteinuria as an Prognosis and Outcome Measure

- ***Choosing the optimal metric-*** **Time averaged/Time-varying; UPCR or UACR; variability as an outcome measure**
- ***Thresholds and* prognosis-** **Must be disease specific. One size does not fit all**
- ***Definitions of Proteinuria Remission-*** **Relationship to mechanistic activity of disease; non- specific anti-protenuric actions of drugs (CNI)**
- ***Quality of Proteinuria-*** **Protein selectivity; FEIgG; Beta2 microglobulin; ATPR**
- ***Effect of Proteinuria*** **(and Hypoalbuminemia) on estimation of GFR**
- ***Role of dual and monotherapy*** **(ACEi/ARB)- Disease specific**

GENERAL PRINCIPLES:

Outcome Measures- A New Paradigm?



GENERAL PRINCIPLES:
Impact of Age/Gender/Ancestry

- Age as a factor in Renal Biopsy interpretation (FGGS); Age as a factor in response rate, complications, drug pharmacokinetics and pharmacodynamics; age and eGFR/ mGFR assesment

- Gender and disease/complications risk

- Ancestry as a determinant of disease risk, therapeutic response and adverse events

GENERAL PRINCIPLES:
Complications

- ***Hypertension***: Goals, Definitions, Management
- ***Proteinuria***: Threshold definitions (Disease specific), goals, non-specfic Management (e.g. RAS, diet, etc)
- ***Dyslipidemia***: Definitons, Goals, Management
- ***Nephrotic Edema***: Management
- ***Thrombophilia and Venous/Arterial Thromboembolism***: Risks, Prevention and Therapy
- ***Infections***- Prophylaxis and Therapy

GENERAL PRINCIPLES:
Adverse Effects of Therapy

- ***Agent Specific Effects***: Avoidance by individualization of therapy based on risk profiling (?pharmacogenomics); prophylaxis

- ***Combination Therapy***

- ***Concomitant drugs***: Drug-Drug interactions

- ***Genetic analysis***: Pharmacogenomics

GENERAL PRINCIPLES:
Therapeutic Monitoring

- ❑ Trough, 2 hour and AUC assesement of individual drug levels (e.g. MMF, CNI)
- ❑ Pharmacodynamic monitoring of specfic drug effects (e.g. CD19, anti-PLA2R, ANCA, C3, C5b-C9)
- ❑ Proteinuria and eGFR/mGFR
- ❑ Repeat Renal Biopsy (indications and timing); disease specific

GENERAL PRINCIPLES:
Pregnancy and Childbirth

- ❑ Effect of Disease on Pregnancy Outcomes (Mother and Child)
- ❑ Effect of Therapy of Fetus (FDA Pregnancy Risk Categories)- Lactation and drugs
- ❑ Effect of therapy on fertility
- ❑ Renal biopsy during Pregnancy

GENERAL PRINCIPLES:
Treatment Costs

- Costs and availability of treatment from a global perspective
- Cost-effectivenss: basic principles- incremental cost-effectiveness – DALY gained per $ expended
- Generics and Bio-similars

GENERAL PRINCIPLES:
Post-Transplant Recurrence

- Definitions of risk and impact on graft survival (Disease Specific)
- Identification of high- and low-risk categories (e.g. Salb in FSGS)
- Prevention and management of recuurent disease

GENERAL PRINCIPLES:

Some New Topic Areas for Consideration

- Social and Ecological determinants of Disease
- Better more Precise eGFR methods; Point-of-care mGFR methods
- Urinary proteomics; Renal biopsy transcriptomics
- Genetic analysis by whole exon or genome sequencing
- Cost-Effectiveness analyses
- „Adaptive“ CPG based on immuno-mechanistic analyses
- Limitations of evidence from RCT- pragmatic trials; n of 1 trials
- Categorization of Adverse Events and Drug-Drug interactions

GENERAL PRINCIPLES:
Potential Research Recommendations

- Need for better and more accurate classifications of disease used by RCT- pathophysiological instead of morphological. Definition of disease, not „patterns of injury“, should be as precise as feasible
- Better and optimal surrogate outcome measures for specific diseases having a patient-centered impact
- RCT of personalized, „adaptive“ strategies for management based on serum/urine biomarkers
- More Cost-Effectiveness research
- Better definition of specifc roles and timing of genomic analyses and serial renal biopsy
- More and better non-invasive assesment of irreversible fibrosis (imaging, urine proteomics) for treatment stratification

GENERAL PRINCIPLES:
Concluding Remarks

- ***The tension between „one-size-fits-all“ generic CPG and individualized therapy based on disease differentiating biomarkers is likely to increase over time!***
- **Response-**
  - **More individualized algorithms („adaptive“ CPG)**
  - **Step-wise cascade of multi-parametric evaluation (serology, genes, proteomics, metabolomics) linked to therapeutiuc interventions**
  - **Outcomes stratified into clinical (proteinuria/GFR/hematuria), immuno-mechanistic (antibodies/mediators) and morphologic (activity/chronicity) domains**

GENERAL PRINCIPLES:

Concluding Remarks

SCAMPS

(***S***tructured **C**linical ***A***ssesment and ***M***anagement ***P***lan)

Care pathways designed around Clinical Practice Guidelines

Farias M, et al Acad Med 2015; 90:143-145 and Sox H Acad Med 2015;90129-132

SCAMPS

(Farias and Sox, Acad Med, 2015)

- **Intended to Complement evidence-based CPG by adding Evidence-Based and Expert Opinion guided *Clinical Care Pathways* (algorithms) for diagnosis, prognosis or therapy**

- **Unlike CPG *multiple decision points* are incorporated, and tools are available to deconstruct CPG's to facilitate SCAMP development**

- ***Starting points* are literature reviews and evidence assessment (shared with CPG)**

- **Tend to be more dynamic and clinically useful for a personalized approach to specific diseases. *"CPGs are the items on the menu-SCAMPS are the recipe"* (Sox H, 2015)**