None response and Loss of Response to treatment with Anti - TNF

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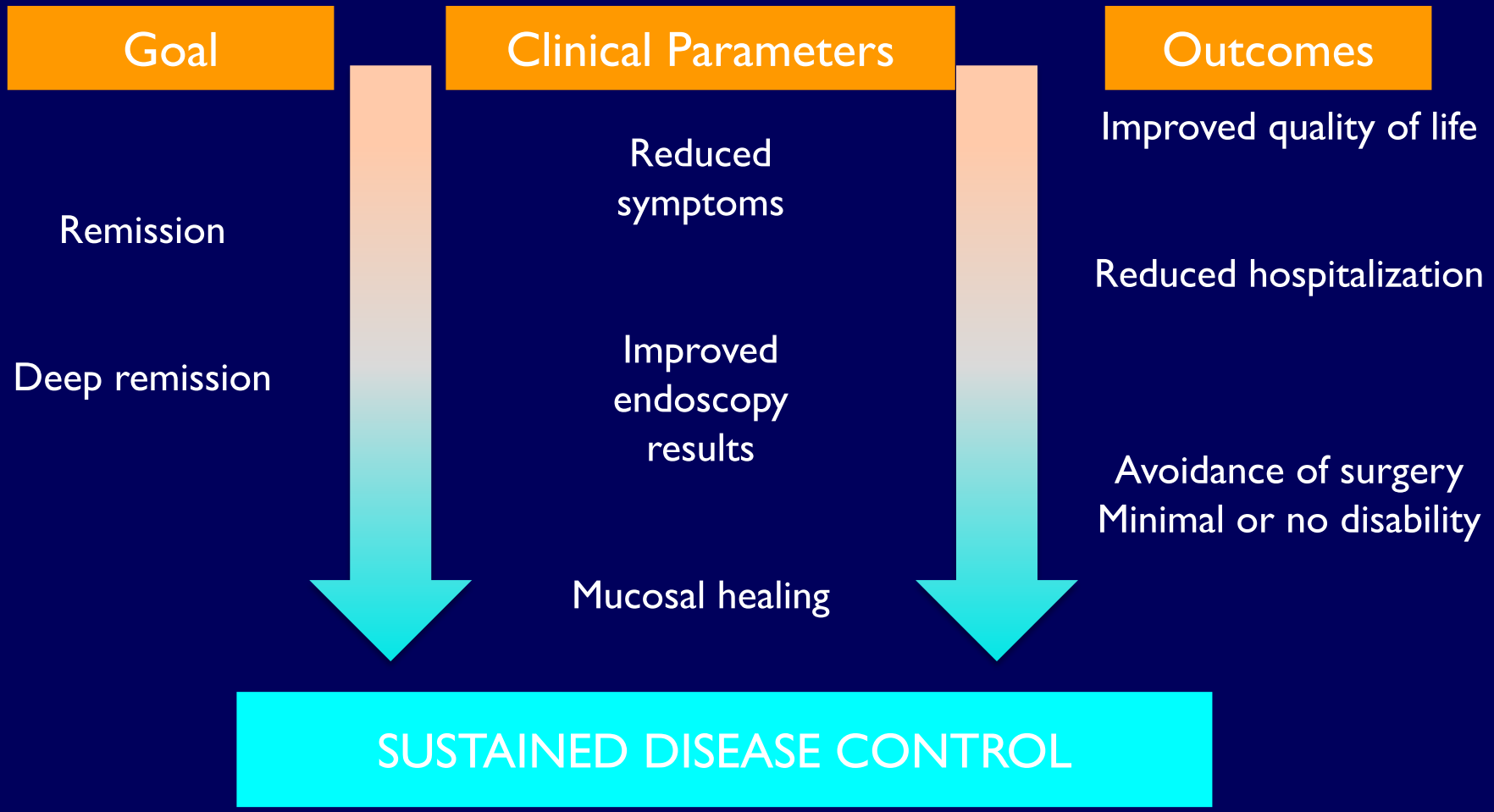
- The pathogenesis of IBD is not well understood.
- Complex interactions between genetic and environmental risk factors contribute to susceptibility.
- The innate immune response appears to be a prerequisite for excessive activation of the adaptive immune system and tissue damage

Current goals of IBD management

- ✔ clarify disease type and severity,
- ✔ induce remission rapidly(eliminate symptoms of disease)
- ✔ Maintain Remission
- ✔ steroid-free remission
- ✔ Mucosal healing
- ✔ change the natural history of IBD, which means to avoid hospitalization and surgery,
- ✔ avoid drug-related and disease-related complications,
- ✔ reduce costs of care.

The ultimate goal of therapy will be the ability to prevent long-term complications of progressive disease such as the development of strictures, fistulae, neoplasia, extraintestinal symptoms, or the need for surgery and Improved quality of life

Goals of IBD Therapy: Sustained Remission, Better Long-term Outcomes



Assess Response to Therapy

- When patients present with persistent or recurrent symptoms suggesting active IBD while on anti-TNF therapy it can present a dilemma for the clinician.

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Assess Response to Therapy

first step is to determine if active IBD is the etiology for the presenting symptoms.

The initial evaluation should rule out

- infectious causes of symptoms mimicking IBD

(*Clostridium difficile*, cytomegalovirus (CMV))

- endoscopic evaluation with colonic biopsies.
- Fecal calprotectin is an ideal choice for this purpose.
- medication side effects including use of NASID , bile acid malabsorption,
- small intestinal bacterial overgrowth (SIBO),
- irritable bowel syndrome (IBS)
- Patient adhesion to thereby

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Assess Response to Therapy

Once it has been determined that active IBD is the etiology based on endoscopic, cross-sectional imaging and/or biochemical markers of inflammation,

the next step is to identify the cause of the treatment failure, as this guides management

patient should be classified as having either

primary nonresponse

or

secondary loss of response

Assess Response to Therapy

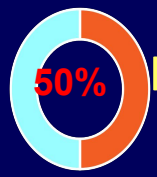
Primary Nonresponders (No Response)

Individuals whose IBD fails to respond to initial induction therapy within 12 wks

Incidence of primary[1] nonresponse

Secondary Nonresponders (Loss of Response)

Individuals with IBD improvement after initial induction, but subsequent Loss of response or development of intolerance to therapy



Incidence of nonresponse with TNF inhibitors

Risk Factor To Develop PNR

CD

- Longer disease duration (>2 years)
- upper gastrointestinal and Small bowel involvement
- Smoking
- Normal CRP
- Genetic mutations (FAS-L, caspase 9)
- a positive p-ANCA
- Younger age at diagnosis
- the need for corticosteroids
- Perianal disease
- Stricturing or penetrating disease

UC

- C-reactive protein (CRP) level above 20mg/liter,
- the need for corticosteroids
- presence of a Mayo score greater than 10
- recent diagnosis (<3 year)

(CD versus UC)

Mechanism OF PNR and SLR

Nonadherence to therapy
Immunogenicity (anti-drug antibodies)
Enhanced drug clearance(non- Immunogenicity)
Altrenat inflammatory pathways
Non-inflammatory complication(structure)
Concurrent infection (C.difficil ,CMV)

Aliment Pharmacol Ther 2016; 43: 30–51

Mechanism OF SLR

Factors Affecting the Clearance of Biologics

Factor	Impact on Pharmacokinetics
Presence of antidrug antibodies	▪ Decreases serum drug concentration ▪ 3-fold increase in clearance ▪ Inferior clinical outcomes
Simultaneous use of immunomodulator	▪ Reduces formation of antidrug antibodies ▪ Increases serum drug concentration ▪ Decreases drug clearance ▪ Improved clinical outcomes
Low Albumin levels	▪ Increases clearance ▪ Worse clinical outcomes
High baseline CRP	▪ Accelerates clearance
Body size	▪ Possible link to increased clearance in patients with high BMI
Gender	▪ Females have reduced clearance

2012;91:635-646 Ordás I, et al. Clin Pharmacol Ther.

Therapeutic drug monitoring
TDM

defined as the assessment of drug concentrations and ADA, is an important tool for optimizing biologic therapy.

Reactive TDM has rationalized the management of PNR and SLR and has proven more cost-effective when compared with empiric dose escalation.

TDM may also improve the cost-effectiveness and safety of biologic therapy via the implementation of a de-escalation strategy in patients with supratherapeutic drug concentrations by reducing the dose, increasing the time interval, and/or stopping the immunomodulator in patients on combination therapy (optimized monotherapy)

Therapeutic drug monitoring
TDM

therapeutic drug monitoring with drug levels and/or antidrug antibody measurement may help distinguish between nonadherence to therapy, immunogenicity and nonimmune clearance of anti-TNF, or inflammatory activity despite adequate anti-TNF levels

MANAGMENT PRIMARY NON-RESPONSE

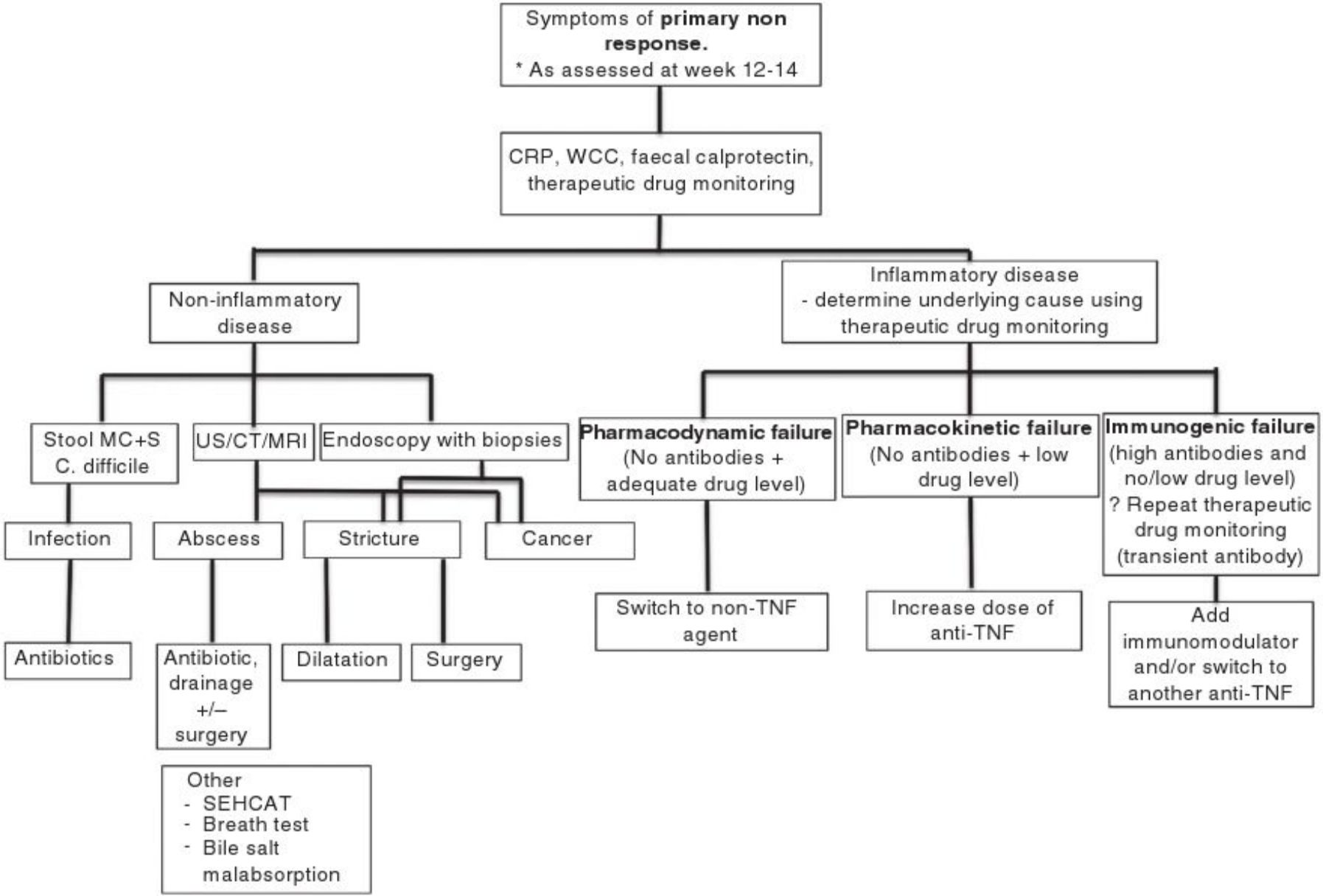
selecting patients who may benefit most from therapy

start medication early

High-dose induction therapy, followed by regularly scheduled maintenance rather than episodic (p.r.n.)therapy, is recommended with all biologics in order to sustain therapeutic levels, avoid immunogenicity, and improve clinicaln outcomes

prospective SONIC trial clearly demonstrated a benefit of combination therapy for patients with earlier disease who were naive to both immunomodulatory and biological therapy.

MANAGMENT PRIMARY NON-RESPONSE



MANAGMENT SECONDARY NON-RESPONSE

Patients who lose response should always be reassessed in order to evaluate disease activity aside from symptoms.

Inflammatory biomarkers such as CRP and fecal calprotectin should be measured and either endoscopic or dedicated imaging must be performed to exclude non-inflammatory explanations for symptoms.

Once inflammation is confirmed, assessing for altered pharmacokinetics and potential immunogenicity may impact and direct treatment decisions.

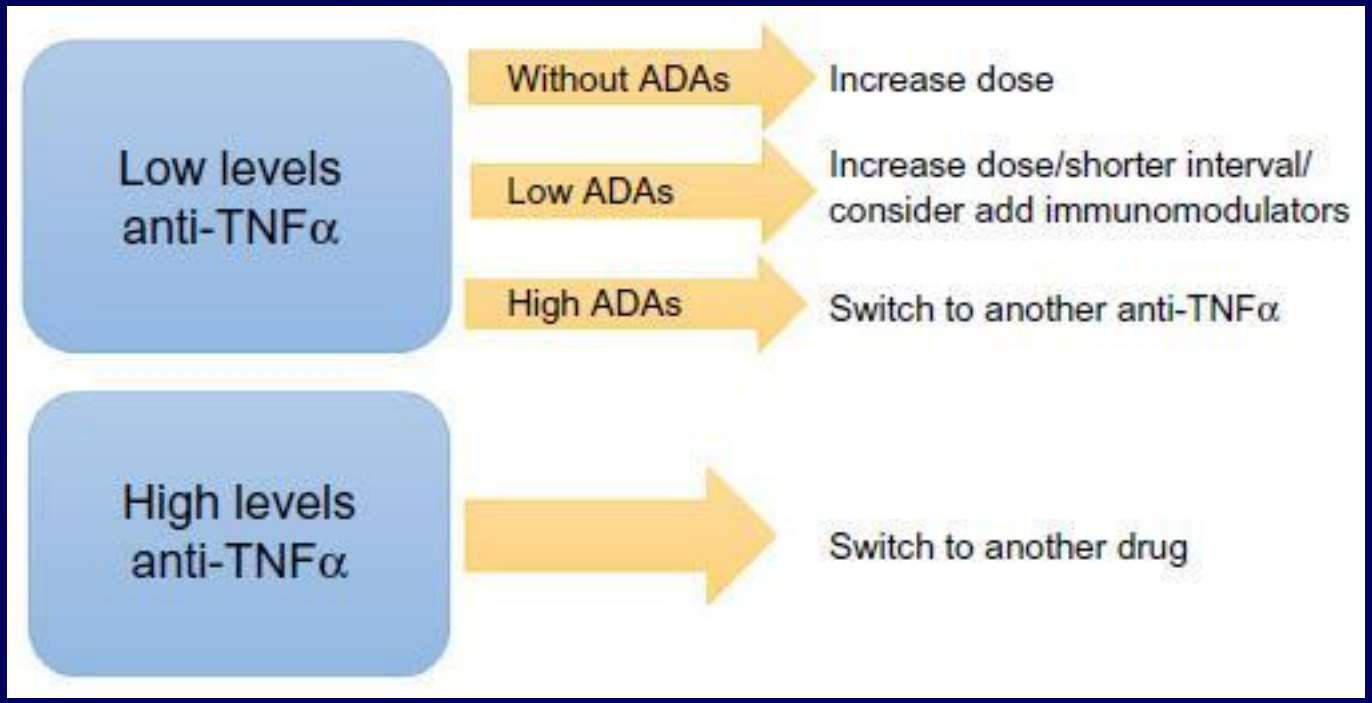
Patients who were found with sub-therapeutic drug levels benefited more from dose escalation compared with switching therapy either increasing doses and/or decreasing intervals between doses are relevant option

MANAGMENT SECONDARY NON-RESPONSE

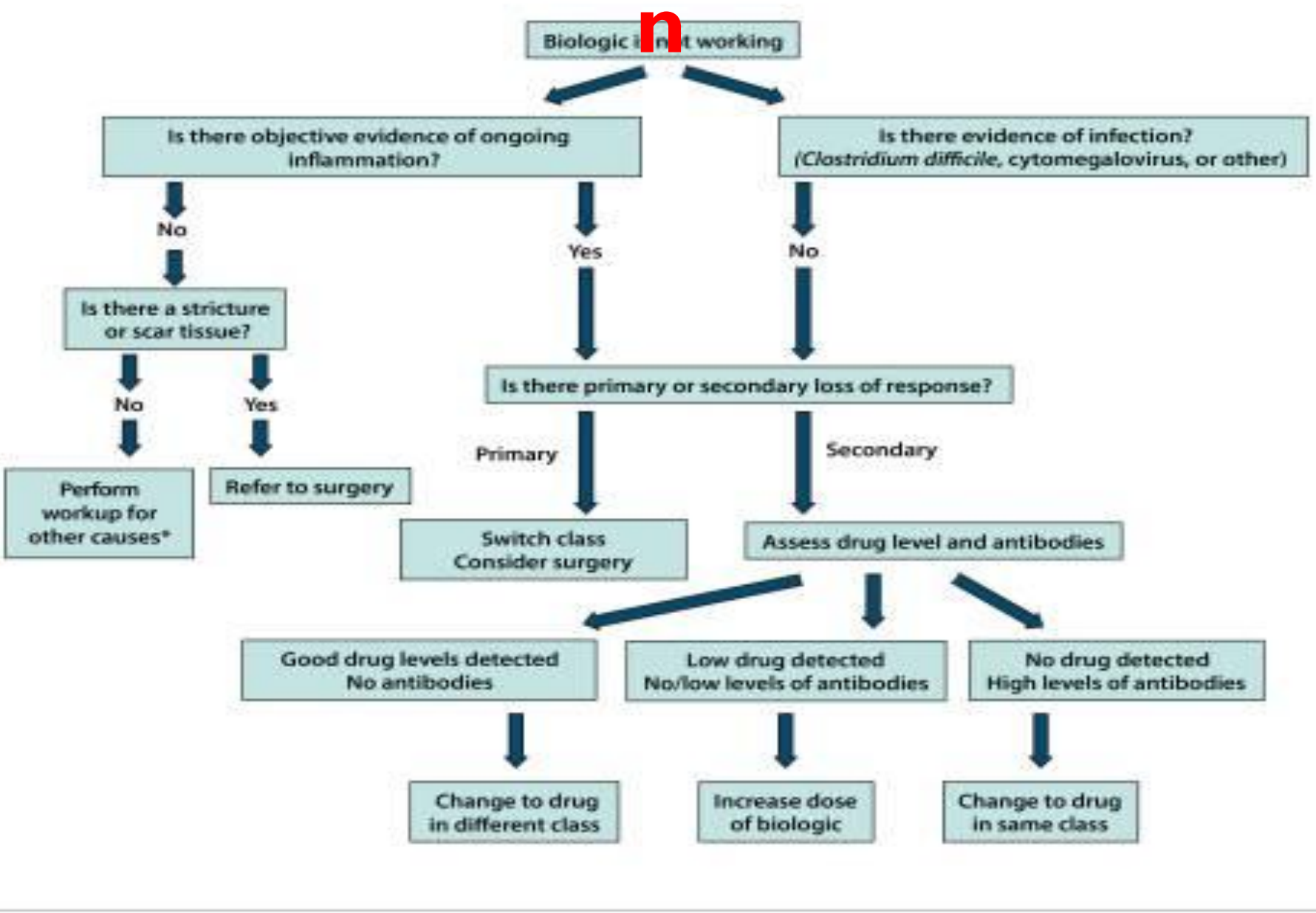
Patients who lose response to a biologic because of immunogenicity, low drug trough levels with high anti-drug antibodies, are most likely to respond to a second agent

within the same class or or use of concomitant immunomodulators to decrease antibody formation or to potentially boost drug levels

it appears that patients who lose response to a first agent are more likely to lose response to a secondand are more likely to profit from switching to a medication with a different mechanism of action (an alternative class)


Low levels anti-TNFα
Without ADAs
Increase dose
Low ADAs
Increase dose/shorter interval/ consider add immunomodulators
High ADAs
Switch to another anti-TNFα
High levels anti-TNFα
Switch to another drug

Conclusion


Biologic is not working
Is there objective evidence of ongoing inflammation?
Is there evidence of infection? (Clostridium difficile, cytomegalovirus, or other)
No
Yes
No
Is there a stricture or scar tissue?
No
Yes
Perform workup for other causes*
Refer to surgery
Is there primary or secondary loss of response?
Primary
Secondary
Switch class
Consider surgery
Assess drug level and antibodies
Good drug levels detected
No antibodies
Low drug detected
No/low levels of antibodies
No drug detected
High levels of antibodies
Change to drug in different class
Increase dose of biologic
Change to drug in same class

TAKE HOME MESSAGE

- to avoid the risk of non-response to a drug,choose the most suitable therapy for each patient at the initiation of the therapy or at loss of response

- CRP and fecal calprotectin is a good predictor of remission and response

- low serum albumin should be considered for early initiation of advanced treatments

- Early TDM during the induction phase could help to identify PK or pharmacodynamic causes of nonresponse or and guide treatment

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TAKE HOME MESSAGE

- to avoid primary nonresponse and secondary loss of response include screening and counselling patients against smoking.
- Treatment early in disease course (within 2 years of disease onset) when disease phenotype is inflammatory
- In nature using intensive combination therapy with an immunomodulator and anti-TNF


Thank
You